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Effectiveness of service models and organisational structures supporting tuberculosis identification and management in hard-to-reach populations in countries of low and medium tuberculosis incidence: A systematic review

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Abstract

Objective To determine which service models and organisational structures are effective and cost-effective for delivering tuberculosis services to hard-to-reach populations.

Design Embase and MEDLINE (1990-2017) were searched in order to update and extend the 2011 systematic review commissioned by NICE, discussing interventions targeting service models and organisational structures for the identification and management of tuberculosis in hard-to-reach populations. The NICE and Cochrane Collaboration standards were followed.

Setting European Union, European Economic Area, European Union candidate countries and Organisation for Economic Co-operation and Development countries.

Participants Hard-to-reach populations, including migrants, homeless people, drug users, prisoners, sex workers, people living with HIV and children within vulnerable and hard-to-reach populations.

Primary and secondary outcome measures Effectiveness and cost-effectiveness of the interventions.

Results From the 19,720 citations found, five new studies were identified, in addition to the six discussed in the NICE review. Community health workers from the same migrant community, street teams and peers improved tuberculosis screening uptake by providing health education, promoting tuberculosis screening and organising contact tracing. Mobile tuberculosis clinics, specialised tuberculosis clinics and improved cooperation between health care services can be effective at identifying and treating active tuberculosis cases, and are likely to be cost-effective. No difference in treatment outcome was detected when directly observed therapy was delivered at a health clinic or at a convenient location in the community.

Conclusions Although evidence is limited due to the lack of high quality studies, interventions using peers and community health workers; mobile tuberculosis services, specialised tuberculosis clinics, and improved co-operation between health services can be effective to control tuberculosis in hard-to-reach populations. Future studies should evaluate the (cost-)effectiveness of interventions on TB identification and management in hard-to-reach populations and countries should be urged to publish the outcomes of their TB control systems.

Systematic review registration PROSPERO *CRD42015017865*.

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Strengths and limitations of this study

- PRISMA and Cochrane Collaboration reporting guidelines for systematic reviews were followed.
- The search was highly sensitive but we might have missed important information as many European countries do not publish their tuberculosis identification and management data in journals, our search focused on Embase and MEDLINE.
- We identified five studies and discuss the results together with the six studies identified by the NICE review to give the complete body of evidence.
- None of the included studies was of high quality and there was high heterogeneity across the studies prohibiting a meta-analysis.

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Introduction

Prevention and control of tuberculosis (TB) is based on early detection and diagnosis of TB followed by effective treatment. In 2015 there were an estimated 10.4 million incident TB cases worldwide, an estimated 4.3 million cases were either not diagnosed, or diagnosed but not reported to national TB programmes.[1] Trends for TB treatment are encouraging, with most notified TB cases completing their treatment successfully; although treatment success rates in some regions, such as the European region, were considerably below the WHO World Health Assembly target of 85%.[1]

In many countries with a low TB incidence (less than ten TB cases per 100,000 population),[2] TB prevails in the big cities where vulnerable and hard-to-reach (under-served) populations are concentrated.[3] These populations, such as people who are homeless (or have insecure accommodation), misuse drugs or are migrants, are at higher risk of contracting TB and are more likely unable or unwilling to seek medical care and comply with the long term TB treatment. Managing TB in those populations is therefore challenging, due to barriers caused by stigma, cultural barriers, poor access to health care services and low levels of accurate TB knowledge.[4,5-7] This therefore requires special efforts. Health care services need to be organised effectively to identify and diagnose TB cases, and to provide adequate treatment and support. This can be organised in different ways, e.g. mainly as hospital-based[8] or health centre-based;[9] including the public sector, private sector,[10] or civil society and other partners.[11] Sometimes, organisation of the services has proven ineffective in managing TB.[12]

The review question of this systematic review with a scoping component was: 'Which service models and organisational structures, including different types of healthcare workers and settings, are effective and cost-effective for delivering TB services to hard-to-reach populations in low- and medium-incidence countries?'

Findings of this review and the previously published review series [4,13] formed the base for the guidance document by the European Centre for Disease Prevention and Control (ECDC) on controlling TB in hard-to-reach and vulnerable populations.[14]

Methods

In 2011, the Matrix Knowledge Group published a review, commissioned by the National Institute for Health and Clinical Excellence (NICE), on effectiveness and cost-effectiveness of service models or structures, focussing on the type of health care worker and setting, to identify and manage TB in hard-to-reach populations. We updated and extended the NICE review,[15] using the same methodology but adjusting the focus by excluding latent TB infection and including additional hard-to-reach populations. The review was conducted following standards described by the Cochrane Collaboration[16] and NICE methods guidelines.[17] Results are reported according to PRISMA guidelines.[18] The review protocol was registered in advance in the database of prospectively registered systematic reviews in health and social care, PROSPERO (*CRD42015017865*).

Selection of studies and data management

The same search strategy as for the previous NICE review[15] and the previous published review by Heuvelings et al.[13] was used, searching Embase and MEDLINE through the Ovid platform. The search was expanded by including all European Union (EU)/European Economic Area (EEA) and EU candidate countries to the Organisation for Economic Co-operation and Development (OECD) countries (see **Box 1**).[15] Two hard-to-reach populations (people living with HIV and children within vulnerable and hard-to-reach populations), were added in addition to the hard-to-reach populations included by the NICE review (migrants including refugees, asylum seekers and the Roma population, homeless people including rough sleepers and shelter users, drug users, prisoners and sex workers).[15] The update of the search conducted for the NICE review[15] covered the period 1 January 2010 (overlapping the end of the search period of the NICE review[15] with a few months) to 24 February 2017. The search for the expanded geographical area and newly included hard-to-reach populations covered a time period from 1 January 1990 (beginning of the search period used in the NICE review[15]) to 24 February 2017.

Reference lists of relevant systematic reviews were scanned. No language restrictions were applied.

Studies focussing on the effectiveness and/or cost-effectiveness of interventions for service models and organisational structures supporting TB identification and management of hard-to-reach populations (see **Box 1**) were included.

Predefined interventions were using more convenient locations (like specialised TB centres, shelters for homeless people or drug users, needle exchange/methadone programme locations, port of arrival, schools or mobile clinics) and peers or health care workers with the same ethnic or cultural background; however, other interventions could also be included if they supported TB identification or management in hard-to-reach populations. TB identification tools, TB diagnostics, incentives, social support, directly observed therapy and treatment of co-morbidities are discussed in another review.[13] In this review we aim to identify the effectiveness of the type of health worker and setting, to identify and manage TB in hard to reach and vulnerable populations.

The comparator was defined during the review process; interventions were compared to a relevant comparator, for example usual care or no intervention, another intervention, or historical comparison.

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Outcomes were defined as any measure of TB identification and management (for example, number of people screened, screening coverage, proportion receiving treatment and treatment completion rate). Effectiveness was defined as an improvement in any measure of TB identification and/or management. Randomised and non-randomised studies were eligible for inclusion.

See **Supplementary Material I** for **the PROSPERO study protocol, Supplementary Material II for** PICOS (Population-Intervention-Comparator-Outcome-Study design) questions and **Supplementary Material III** for the complete search strategy and search results.

Data extraction, data items, and synthesis

Identified citations were entered into an EndNote database, and duplicates removed (EndNote X7.1, Thomson Reuters 2014). The inclusion criteria were piloted and refined using the first 25 citations. Double screening was conducted by one reviewer screening 100% of the citations (CCH) while another two reviewers screened 50% of the citations each (PFG, SGdV) for inclusion on title and abstract. Disagreement was resolved by discussion. Full text files of included citations were retrieved; irretrievable articles (not available after attempts online, from the university library or through contacting authors) were excluded. Two reviewers assessed full text records for inclusion (CCH, PFG). Disagreement was resolved by discussion. Agreement after screening on title and abstract was 99.6% with an inter-rater reliability (Cohen's kappa) of $\kappa = 0.985$.

Data extraction forms from the NICE review[15] were used to extract information on participant characteristics, settings, types of services/organisational structures, types of healthcare workers delivering the service, outcome measures, methods of analysis and results. For one study data extraction was conducted by two reviewers (CCH, PFG) independently. For the remaining studies, data extraction was conducted by one reviewer (CCH) and checked by a second (PFG); disagreement was resolved by discussion. In one case, the study author was contacted to verify data and obtain additional data.[19]

To facilitate comparability, data synthesis was structured in a similar way to that of the NICE review.[15] Studies were divided into those examining service models and organisational structures for TB identification (screening) and those examining service models and organisational structures for TB management (treatment and support) in hard-to-reach populations. Data were analysed narratively, and appropriateness of meta-analysis considered. Findings were reported as stated by the study authors.

Risk of bias in individual studies and overall strength of evidence

The modified NICE Quality Assessment Tools[17] (based on the Graphical Appraisal Tool for Epidemiological studies) were used to assess quality and risk of bias of included studies. This included an assessment of selection of study sample, minimisation of selection bias and contamination, controlling confounding, outcome measurements, analytical methods and risk of bias. Two reviewers (CCH, PFG) assessed one study independently; the remaining studies were assessed by one reviewer (CCH), and checked by a second reviewer (PFG). Any disagreement was resolved by discussion. Studies were given a quality rating based on the quality assessment: high quality [++], medium quality

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[+], or low quality [-]. The strength of the evidence was assessed and reported as described in the previous NICE review[15] (**Supplementary Material IV**).

Results

Of the 19,720 citations identified by the literature search five studies were included in this review (**Figure 1**).[11,19-22] These five studies are in addition to the six studies[23-28] included in the NICE review.[15] The results section in this paper focuses on the evidence of the five studies identified in our updated review. The evidence statements (presented in **Supplementary Material IV**) summarise evidence identified in terms of consistency, quality and applicability, combining evidence from the NICE review[15] and this update.

All five studies were conducted in the EU; two in the United Kingdom (UK),[19,22] one in Germany,[20] one in Portugal[11] and one in Spain.[21] Two studies focussed on homeless people,[19,20] one on homeless people and drug users,[22] one on drug users alone[11] and one on migrants.[21] Four studies[5,19-21] addressed the influence of the type of healthcare worker on TB identification and TB management and one study focussed on the influence of different settings on TB identification.[22] A variety of study designs were included; one study was a prospective cluster randomised controlled trial (RCT),[19] one was an economic evaluation using a compartmental model of treated and untreated active TB cases[22], and three studies were retrospective comparison studies.[11,20,21] Study characteristics of included studies are described in **Table 1**. The data extraction forms by study are presented in **Supplementary Material V**.

None of the included studies in this review had a low risk of bias, three studies[19,21,22] had a medium risk of bias, the other two studies[5,20] were assessed as having a high risk of bias (**Supplementary Material VI)**.

We did not perform a meta-analysis due to study heterogeneity. Results were synthesised narratively.[29]

Main outcomes for services structures and organisational models for TB identification among hard-to-reach populations, combined with the findings of the NICE review,[15] are summarised in **Table 2**. For full evidence statements, see **Supplementary Material IV**.

Three studies[19-21] compared the effect of the type of healthcare worker on TB identification.

In the UK, a cluster-randomised trial found that peer educators working together with shelter staff to encourage homeless people to participate in a TB screening programme using mobile X-ray units (MXU), did not improve screening uptake compared to encouragement by shelter staff only (respectively 40%, interquartile range [IQR] 25-61 versus 45%, IQR 33-55; adjusted risk ratio [aRR] 0.98, 95% confidence interval [95% CI] 0.80 to 1.20).[19] Control sites were not 'naïve' for peer intervention which could have caused contamination of the control sites and contributed to the negative finding.

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In Germany, introduction of TB education and promotion of voluntary chest X-ray (CXR) screening at least once every two years by community health workers (CHWs) improved screening uptake in homeless people and drug users. Annual screening coverage increased from 10.0% at the beginning of the study period (2002-2004) to 15.0% during the middle part of the study period (2004-2006), the last part of the study period had a 13.4% annual screening coverage (2005-2007). Screening once every two years increased screening coverage from 18.0% (2002-2004) to 26.4% (2004-2006). Coverage was 23.4% at the third and final study period (spanning 2005-2007).[20] The authors did not test for statistical significance, and denominator data (the number of homeless people and drug users in the study area) were estimated.

In Barcelona, Spain, contact tracing organised by CHWs coming from the same migrant community as the person diagnosed with TB, improved contact tracing among migrants to 66.2% (2003-2005) compared to 55.4% (2000-2002) in the period before the implementation of the intervention using CHWs (adjusted odds ratio [aOR] of an index case having their contacts screened before and after the intervention was 1.8, 95% CI 1.3 to 2.5, $p<0.001$).[21] Identification and tracing of at least one contact was taken as appropriate contact tracing, where all contacts at risk should be traced to detect and treat TB transmission early. The population characteristics varied, the age and country of origin was different between both periods. The importance of contact tracing is to identify cases early to reduce transmission, the authors did not report if any of the contacts traced had active TB.

Two studies[11,22] evaluated the effect of the type of healthcare worker and the setting on TB identification and TB management.

In Portugal, improved co-operation of 'key partners' (street teams, TB clinics, drug user support centres, local public health department and local hospital) for TB identification and management in drug users was evaluated in a before-and-after study. Representatives of all 'key partners' (authors' term) worked on improving policies, clinic screening procedures and co-operation. Key partners were trained in identifying drug users in their population; and offering health promotion, notification cards, free transport to the TB clinic, free medical and substance abuse care, directly observed therapy (DOT) for active TB cases, identification of non-compliant patients and the cause of non-compliance, and tailor-made strategies to improve compliance. This resulted in an increase of TB screening uptake; from 52 drug users being screened before the intervention (2001-2003 when there was no active screening policy) to 465 drug users screened thereafter (2005-2007). Of all people misusing drugs taking-up screening, the proportion without TB symptoms increased from 41.6% to 93.5% (OR = 21.76; 95% CI 13.03 – 36.33) indicating improved TB awareness and access to screening facilities for drug users. Of all drug users with active TB, the proportion identified by screening increased from 13·4% to 61·0% (OR 10·1; 95% CI: 4.44 – 23.0). Treatment default rates decreased from 35.4% to 10.2% (OR 0·.21, 95% CI 0.08-0.54), compared to the period before the intervention (2001-2003) when TB treatment was not compulsory and compliance was stimulated by TB education and providing information on the importance of treatment completion.[11] Although the absolute number of drug users screened increased, information on the screening coverage was not available as denominator

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data were not provided. Another limitation is that the results were not adjusted for confounding factors, baseline characteristics might have been different as the two cohorts were recruited over different time periods and participation was voluntary which may have led to selection bias.

In the United Kingdom, the effectiveness and cost-effectiveness of the 'Find and Treat' service (raising awareness of TB screening and providing a mobile TB screening and treatment service) for homeless people and drug users was evaluated and compared to people (with a history of homelessness, imprisonment, drug abuse or mental health problems) self-presenting to a London TB clinic receiving standard TB care at the clinic.[22] The authors estimated that 22.9% of the patients detected by the 'Find and Treat' service with the longest first symptom-to-detection time would not have self-presented plus 35.4% were asymptomatic at time of detection and would not have self-presented, only part of the asymptomatic patients would self-present to a TB clinic at a later stage when symptoms would have developed. The 'Find and Treat' service had a higher treatment completion rate (67.1% versus 56.8%), and a lower lost to follow-up rate (2.1% versus 17.2%) compared to the control group receiving standard TB care at a TB clinic. The authors concluded that the 'Find and Treat' service was cost-effective, when using the threshold used by NICE of £20,000 to £30,000/QALY gained, with an incremental cost ratio of £18,000 per QALY gained for the TB screening service and £4,100 per QALY gained for the TB management service. This study has a few limitations: firstly, it is a non-randomised study, secondly the 'Find and Treat' service identifies extremely hard-to-reach populations of which some would never self-present therefore the findings could be even better in less hard-to-reach populations, and thirdly the economical evaluation is based on a compartmental model that does not take secondary transmission and drug-resistance into account.

Discussion

To tackle TB and disrupt transmission in high-income, low TB incidence settings, improvement of TB care in hard-to-reach populations is of vital importance. In this updated review, five studies,[11,19-22] published between 1 January 2010 and 24 February 2017, evaluating effectiveness of services models and organisational structures supporting TB identification and management of hard-to-reach populations, were identified in addition to the six studies considering active TB[23-28] identified by the NICE review.[15] Only one study[22] evaluated cost-effectiveness. Although the evidence from two reviews is limited, it highlights those interventions that are likely to be effective and those that have no clear evidence of being effective (**Table 2**). For development of the ECDC guidance document,[14] a scientific panel compiled by ECDC carefully considered these findings. Their main suggestions for action were to involve CHWs or peers to improve TB screening uptake and TB treatment completion among homeless people[20] and drug users;[5,20,23] to use outreach teams to improve TB screening uptake and TB treatment completion among vulnerable populations;[22] and to strengthen relationships and good collaboration between health care workers, peers, communities, and patients to improve treatment outcome among vulnerable populations.[5,20,22,23] The updated systematic review provided evidence for all suggestions except for using peers to improve screening uptake. This is in contrast to an American

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study[23] included in the original NICE review,[15] which showed that peers improved contact tracing and treatment adherence among drug users.

Strengths and limitations

PRISMA and Cochrane Collaboration reporting guidelines for systematic reviews were followed. Established screening protocols were used, including double screening, and the search was highly sensitive. The methodology from the previous NICE review[15] was followed, in order to connect this update and, so, describe the full body of relevant evidence. High quality evidence is lacking. Only one[23] study from the NICE review[15] was considered to be of high quality, all other studies had some risk of bias (five medium risk[19,21,22,24,26] and five high risk[11,20,25,27,28]). Therefore, only limited conclusions can be drawn. Most studies lacked identification and adjustment for confounding factors and the use of appropriate analytical methods. In addition, many studies were biased, particularly with regard to potential selection bias. A meta-analysis could not be performed, because of heterogeneity across the studies. Gaps in evidence exist; no studies focussing on children within vulnerable and hard-to-reach populations, or on people living with HIV or sex workers were identified. Only three studies provided economic data; one study identified by this review,[22] and two[25,27] by the NICE review.[15]

Our search focussed on publications in databases Embase and MEDLINE. Many European countries have strong organisational structures for TB identification and management, but these countries did not publish their data on these organisational structures in journals, which may have caused a publication bias. Comparing findings of the NICE review[15] with this review comes with some limitations. For the NICE review only 10% of the citations were double screened,[15] compared to 100% for this updated review, therefore studies conducted between 1990-2010 might have been missed. The NICE review focussed their recommendations on the population in the United Kingdom,[15] and this review focussed on populations in high-income, low TB incidence countries. Further methodology was identical.

The evidence identified by this review and the previous NICE review[15] along with evidence presented in a review series covering the barriers and facilitators of seeking TB care,[6] and the effectiveness of interventions for TB identification and management in hard-to-reach populations,[13] was used to develop the ECDC guidance on improving TB identification and management among hard-to-reach and vulnerable populations in Europe.[14] ECDC recommended that implementation of the interventions is context-specific; it depends on the setting, target population, resources available and health-care systems in place. Interventions focussing on one specific hard-to-reach population might not work in another hard-to-reach population, therefore, the interventions have to be adapted and re-assessed per target population.[14] Given the scope of this review, considering settings across Europe, findings presented here are potentially relevant to any low-incidence region, and are relevant to other institutions/governmental organisations seeking to improve service structures for TB identification and management among hard-to-reach populations.

Characteristics of different hard-to-reach populations and their TB epidemiology vary per country and setting. Challenges in identification and management of TB should be identified and targeted, tailored

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to the specific setting and hard-to-reach population. These TB interventions could be integrated within broader programmes targeting specific populations. A follow-up systematic review should include information from national public health services about their organisational structures for TB identification and management. National public health services are urged to regularly analyse their organisational structures for TB identification and management and publish this data.

Efforts to improve quality of research on service models and organisational structures should be made, even though it is often challenging to perform 'clean', unbiased, and un-confounded trials in hard-to-reach populations, as attrition rates are often high, and confounding factors are plentiful. This includes conducting (cluster) randomised controlled trials and before-and-after studies where appropriate, recruiting an adequate number of participants, using relevant control groups, and minimising selection bias. Standardised case definitions for hard-to-reach populations should be created. Feasibility, effectiveness, cost-effectiveness and impact of interventions should be evaluated. Mathematical economic models can be used to evaluate costs.[14]

Conclusions

Identification and management of TB in hard-to-reach populations is suboptimal.[2] Therefore, service models and organisational structures to identify and manage TB in hard-to-reach populations should be improved and evaluated regularly.

Our systematic review, in conjunction with the original NICE review[15] provides limited evidence , due to the lack of high quality studies, that interventions such as using peers and CHWs; mobile TB services, specialised TB clinics, screening, or active case finding in non-healthcare settings, as well as improved co-operation between key services can help to improve TB identification and management.

Further research should be undertaken to evaluate other effective and cost-effective ways to identify and manage TB in hard-to-reach populations and countries with good TB control systems are urged to evaluate their system and publish the data.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and all except for MPG and BS declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MPG reports grants from ECDC, for the conduct of part of the study. BS reports that NICE - her employing organisation - has published guidance in this area.

Authors' contribution

RS conducted the literature search. CCH, SGdV and PFG performed the study selection. CCH, and PFG collected the data, performed quality/risk of bias assessment and synthesised the data. CCH prepared the manuscript and supplementary files. MPG and MvdW supervised the whole process and contributed to the work. All authors were involved in interpretation of the data, and the writing of the manuscript. All authors contributed to, and endorsed the final version of the manuscript. MPG is guarantor.

Ethics

Ethics approval was not required for this systematic review.

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Statement of independence of researchers from funders

The funder of the study was involved in study design, data interpretation, and reporting. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Data extraction forms and quality assessment forms are available from **Supplementary files V** and **VI**.

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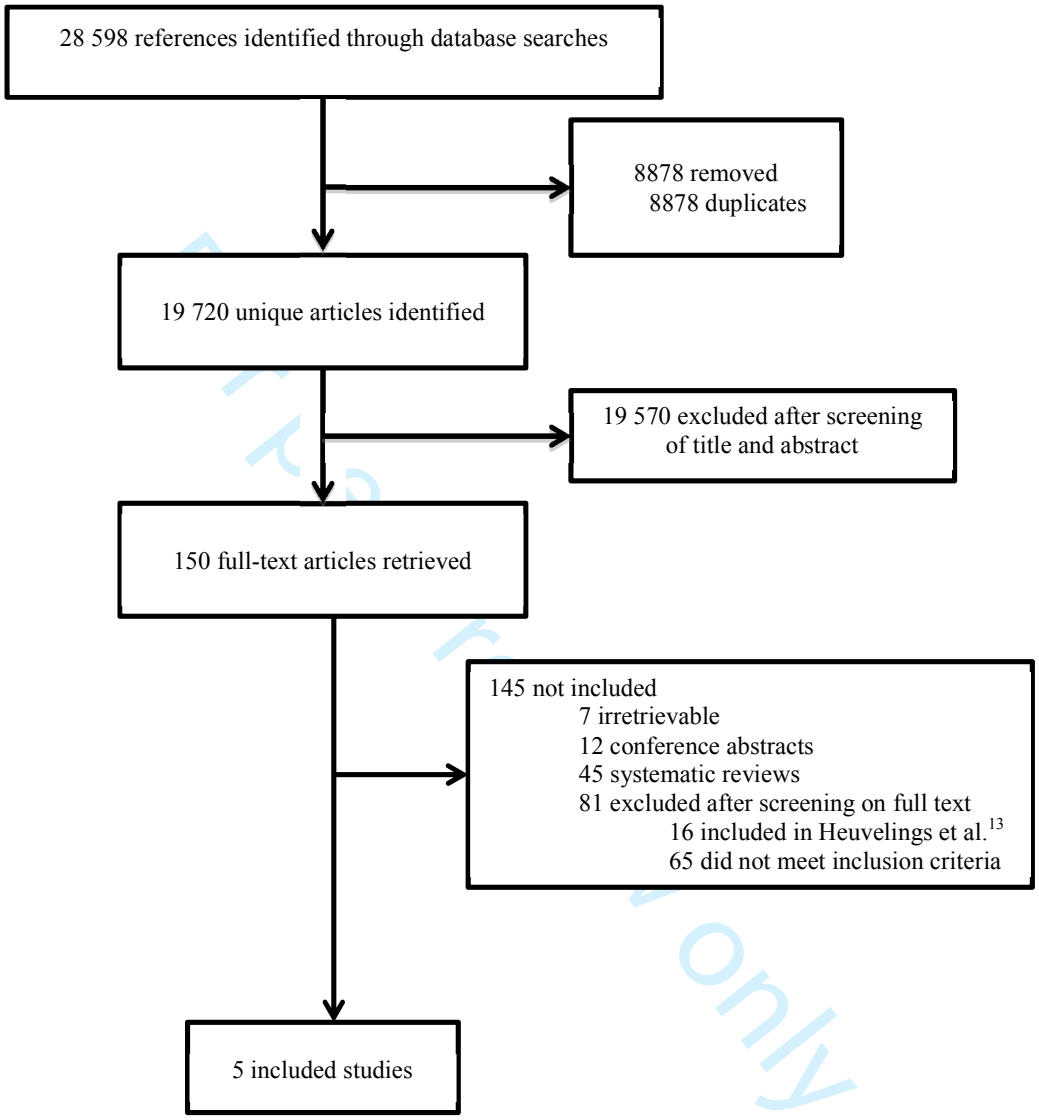
Figure 1. Study selection process



For the Organisation for Economic Co-operation and Development (OECD) countries and hard-to-reach populations discussed in the previous NICE review,[13] the study period covers 1 January 2010 to 24 February 2017
For the newly included European Union (EU)/European Economic Area/EU candidate countries, and the newly included hard-to-reach populations (people living with Human Immunodeficiency Virus (HIV) and children within vulnerable and hard-to-reach populations, the study period covers 1 January 1990 to 24 February 2017.

Table 1. Characteristics of studies applying different service models and organisational structures to improve TB identification and TB management

First Author (year) country	Population	Aims	Intervention	Comparator	Study design	Outcome measure	Quality score
TB identification (studies identified by this review)							
Jit et al. (2011)[22] United Kingdom	Homeless people and drug users	To assess the effectiveness and cost-effectiveness of the Find and Treat service for diagnosing and managing hard-to-reach individuals with active TB in London.	Period 2007-2010: Find and Treat service: - screening by MXU - peers raising awareness - treatment support	Passive case detection and standard treatment at a London TB clinic	Observational and cost-effectiveness study	Identified TB cases, treatment completion, lost to follow-up, incremental costs from healthcare taxpayer perspective	+
Duarte et al. (2011)[11] Portugal	Drug users	To evaluate the effect of an intervention with key partners (TB clinic, drug users support centres, shelters, street teams, public health department and hospital) delivering promotion of health-seeking behaviour, eliminating potential barriers for TB screening at a chest clinic and DOT, on identifying TB cases and treatment compliance.	Improved co-operation of key partners (2005-2007): - health education and screening promotion - improved screening procedures - implementation of DOT - free TB care and transport - providing medical and drug abuse treatment - active follow-up of non-compliant patients, the key partners worked together to reach the patient, identify the cause and organise suitable treatment strategies	Period before the intervention (2001-2003): - no active screening policy - referral to chest clinic after discharge from hospital - treatment not compulsory - information about disease and treatment given to improve compliance - psychosocial support - free TB treatment, transport and breakfast	Before-after study	Identified TB cases and treatment compliance	-
Goetsch et al. (2012)[20] Germany	Homeless people and drug users	To estimate the coverage of a low-threshold CXR screening programme for pulmonary TB among illicit drug users and homeless persons.	CHWs providing TB education and promoting voluntary CXR screening 1-2x/year	Comparing the beginning of the 5 year intervention period with the end (2002-2007)	Retrospective effectiveness study	Screening coverage	-
Ospina et al. (2012)[21] Spain	Migrants	To evaluate the effectiveness of an intervention with community health workers to improve contact tracing among migrants	CHWs active follow up of cases and contacts, including visits of the cases at home, accompanying at outpatient appointments, providing counselling and information on treatments (2003-2005)	Pre-intervention period (2000-2002)	Before-after study	Number of migrants that were included in contact tracing	+

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Aldridge et al. (2015)[19] United Kingdom	Homeless people	To compare TB screening uptake between current practice of encouraging homeless people by shelter staff and encouragement by shelter staff plus volunteer peer educators.	Encouragement of TB screening by peers in addition to shelter staff	Encouragement of TB screening by shelter staff only	Cluster randomised controlled trial	Screening uptake	+
TB identification (studies identified by the previous NICE review[15])							
El-Hamad et al. (2001)[24] Italy	Migrants	To compare the completion rates of screening procedures for TB infection among undocumented migrants at specialised TB units and non-specialised health clinics	TB screening at specialised TB clinic	TB screening at a general health service for migrants	Prospective cohort	Screening completion	+
Bothamley et al. (2002)[25] United Kingdom	Migrants and homeless people	To compare the yield and costs of TB screening in three settings: a new entrants' clinic within the port of arrival (POA) scheme; a large general practice; and centres for the homeless	TB screening at a general practice (GP)	TB screening at POA and at homeless centres	Cost analysis	Cost per person screened per case of TB prevented	-
Deruaz & Zellweger (2004)[28] Switzerland	Migrants, alcohol or drug users, homeless people and prisoners	Evaluation of first experience of the DOT programme for TB introduced in the Canton of Vaud in 1997	1. Full DOT 2. DOT delivered at TB clinic	1. Partial DOT (DOT only first 2 months of treatment) 2. DOT delivered at social outreach site	Before-after study	Adherence to treatment and outcome	-
Miller et al. (2006)[26] United States	Homeless people and prisoners	To evaluate and compare the efficiency of a non-state-law-mandated TB screening programme for homeless persons with a state-law-mandated TB screening programme for prisoners	Non-state-law-mandated TB screening programme for homeless persons	State-law-mandated TB screening programme for prisoners	Retrospective comparison of the cost and health impacts	TB cases averted and cost	+
Ricks (2008)[23] United States	Drug users	To compare the effectiveness of using peers versus 'standard' public health workers to coordinate TB treatment	Enhanced case management by peers	Limited case management by heath care professionals	Randomised controlled trial	Adherence to treatment	++

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Mor et al. (2008)[27] Israel	Migrants	To examine the effectiveness and cost-effectiveness of pre-migration screening and post-migration screening at POA	Pre-migration screening	Post-migration screening	Retrospective cohort analysis	Active TB cases, time between migration and diagnosis, cost-savings	-

List of Abbreviations

CHW = community health worker; CXR = chest X-ray; C = comparator group; DOT = direct observed treatment; GP = general practice; I = intervention group; IRIS = immune reconstitution inflammatory syndrome; IVDU = intravenous drug users; MXU = mobile X-ray unit; *n* = number of participants; QALYs = quality adjusted life years; POA = port-of-arrival; RCT = randomised controlled trial; TDM = therapeutic drug monitoring; TB = tuberculosis

Study quality: high quality [++], medium quality [+], or low quality [-]

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Table 2. Effectiveness of service models and organisational structures interventions to improve TB identification and TB management

Population	Intervention (I)	Comparator (C)	Studies (first author, year, country)	No. of participants I	C	Comparison	Outcome	Risk of Bias
Homeless people Drug users	Health/TB education and promotion of screening by street teams, drug users support centres, shelters and CHWs	Beginning of the intervention when CHWs were just introduced No active screening policy	Goetsch et al. 2012 (Germany)[20] Duarte et al. 2011 (Portugal)[11]	465	125	Retrospective comparison over intervention period Retrospective before-after comparison	Improved annual TB screening uptake among homeless people and drug users (from 10.0% to 15.0% at the peak).[20] The percentage of all drug users with active TB identified by screening increased from 13.4% to 61.0% (OR 10.1 [95%CI 4·44-23·0]).[11]	High$_2$ High$_3$
Homeless people	TB education and promotion of screening by peers and shelter staff	TB education and promotion of screening by shelter staff only	Aldridge et al. 2015 (United Kingdom)[19]	1150	1192	Comparing randomised intervention cluster with comparator cluster	No difference in screening uptake (I = 40% [IQR 25-61] versus C = 45% [IQR 33-55], aRR= 0.98 [95%CI 0.80-1.20]).	Medium$_4$
Migrants	Pre-migration screening	Post-migration screening at POA	Mor et al. 2008, cited in the NICE review (Israel)[27]	162	105	Retrospective Intervention versus comparator comparison	Reduced the risk of developing TB in the new country and was cost-effective (0.28% of the pre-migration versus 0.32% of the post-migration screening migrants developed TB; RR 0.82 p<0.01)). The detection period was shorter as well (193 days versus 487 days between entry and diagnosis; OR=0.72 [95%CI 0.59-0.89] p=0.002).	High$_8$
Prisoners and homeless people	TB screening in a prison	TB screening at a homeless centre	Miller et al. 2006, cited in the NICE review (United States)[26]	22920	822	Retrospective comparison of two cohorts	No difference in screening uptake (94.7% in prison versus 95% in homeless centre p=0.179) but higher proportion of active TB cases were identified at the homeless centre (1.2% versus 0.03% at a prison setting, p<0.001)	Medium$_9$
Homeless people and migrants	Active case finding by symptom-based questionnaire at homeless centres	Active case finding by symptom-based questionnaire at POA	Bothamley et al. 2002, cited in the NICE review (United Kingdom)[25]	262	199	Cost analysis	Active case finding at POA was most cost-effective (costs per person screened for every case prevented at POA £10.00, at homeless centre £23.00).	High$_{10}$
Migrants	Active case finding at a specialised TB clinic using 2 visits	Active case finding at a general primary care clinic, with referral for CXR, using 3 visits	El-Hamad et al. 2001, cited in the NICE review (Italy)[24]	749	483	Prospective intervention versus comparator comparison	Improved screening completion among migrants (85.6% in TB clinic versus 71.4% at primary care clinic, p = not reported; OR=2.57 [95%CI 1.92-3.42]).	Medium$_5$

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Drug users Migrants	Contact tracing by peers or CHWs from the same migrant community	Peers versus other health care workers Normal practice before introducing CHWs	Ricks 2008, cited in the NICE review (United States)[23] Ospina et al. 2012 (Spain)[21]	48 388	46 572	RCT Before-after comparison	Improved contact tracing among drug users (75% by peers versus 47% by healthcare workers, p = 0.03)[23] and migrants (from 55.4% without CHWs to 66.2% with CHWs; aOR 1.8 [95%CI 1.3-2.5] $p<0{\cdot}001$).[21]	Low Medium[1]
Drug users and homeless people	Mobile TB screening and treatment service at convenient location in the community	Passive case detection and management at a TB clinic	Jit et al. 2011 (United Kingdom)[22]	48	252	Prospective intervention versus comparator comparison plus economic evaluation	Improved TB identification among homeless people and drug users; particularly in asymptomatic patients (35.4% extra identified) and those that delay seeking health care (22.2% extra identified). Higher treatment completion rate (67.1% versus 56.8%) and lower lost to follow-up rate (2.1% versus 17.2%). Both parts of the service are cost-effective (screening = £18,000/QALY gained, treatment is £4,100/QALY gained)	Medium[6]
Drug users	Enhanced case management by peers	Limited case management by regular health care workers	Ricks 2008, cited in the NICE review (United States)[23]	48	46	RCT	Improved treatment completion in drug users (85% by peers versus 61% by health care workers, RR=2.68 [95%CI 1.24-5.82] p=0.01).	Low
Drug users	DOT and active follow-up of non-compliant patients by 'key partners'	Non-compulsory TB treatment and education about TB disease and treatment to improve compliance	Duarte et al. 2011 (Portugal)[11]	465	125	Retrospective before-after comparison	Reduced treatment default rates (from 35.4% to 10.2%; OR 0.21 [95%CI 0.08-0.54]).	High[2]
Migrants, drug users, homeless people and prisoners	DOT at a convenient location in the community	DOT at a health clinic	Deruaz & Zellweger 2004, cited in the NICE review (Switzerland) [28]	36	18	Retrospective before-after comparison	No significant difference in successful treatment outcome, treatment completion and cure rate (85.2% at convenient location versus 92.6% at health clinic, p=0.67)	High[7]

List of Abbreviations

aOR = adjusted odds ratio, aRR = adjusted risk ratio, C = comparator group, CHWs = community health workers, DOT = directly observed treatment, I = intervention group, IQR = interquartile range, OR = odds ratio, POA = port-of-arrival, RCT = randomised controlled trial, TB = tuberculosis, 95%CI = 95% confidence interval

Footnotes Risk of Bias:

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[1] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). Contact tracing of only one contact was enough to be called contact tracing, and the ultimate aim of contact tracing (increase cased detection and reduce transmission) was not analysed in this study.
[2] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). Denominator not given therefore unable to calculate screening coverage.
[3] = Risk of selection bias as participation was voluntary. Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). No statistical test used to show statistical significance of the findings, an estimated number was used for the denominator.
[4] = Most comparator sites were not naïve for peer intervention, no individual information of the participants was collected, the characteristics between the two groups might have been significantly different.
[5] = Not adjusted for difference in baseline characteristics.
[6] = Study was designed to evaluate the cost-effectiveness, no statistical test used to evaluate statistical significant findings. The 'Find and Treat' service identifies extremely hard-to-reach populations that would never self-present, the findings would underestimate the benefit of the service. The economical evaluation is based on a compartmental model that does not take secondary transmission and drug-resistance into account,
[7] = Risk of bias due to difference in collecting treatment adherence outcome at the health clinic a nurse recorded treatment adherence at time of visit, in the social outreach group a health care worker was interviewed up to 6 months after treatment completion and was asked about the treatment adherence, risk of recall bias. Not recorded how many people per setting received 6 months of DOT (full DOT) and how many received 2 months of DOT and 4 months of self-treatment (partial DOT), what was another intervention in this study. Allocation to setting was based on needs of participants what might have caused bias.
[8] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods), pre-migration group had a shorter follow-up period than post-migration group what may have influenced the detection of number of TB cases in the pre-migration group.
[9] = Unclear if the differences in outcome was caused by the setting or by the different methods or to differences in TB prevalence in the different populations.
[10] = TB prevalence might be different in the different populations as the costs are calculated per active case detected this is a major issue, there were only 3 active TB cases detected, all in the POA group. The economic perspective used was not reported and the costs of identification were not discounted.

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Box 1: Inclusion/exclusion criteria for this review

Inclusion criteria:

- Discussing service models and organisational structures, different types of healthcare workers and settings for delivering TB services to hard-to-reach populations;
- Having been conducted in any of the EU/EEA countries (only updated review), the candidate countries* (only updated review) and the other OECD countries**
- Having been published in 2010 or later for the OECD countries**
- Having been published in 1990 or later for the EU/EEA countries and the EU candidate countries* not being one of the OECD countries (only updated review)
- Including data from any hard-to-reach population:
    - homeless people
    - people who abuse drugs or alcohol
    - sex workers
    - prisoners or people with a history of imprisonment
    - migrants, including vulnerable migrant populations such as asylum seekers, refugees and the Roma population
    - children within vulnerable and hard-to-reach populations (only updated review)
    - people living with HIV (only updated review)
- Present quantitative empirical data
- Being a (cost)-effectiveness study, or any other type of quantitative primary research, discussing (cost-)effectiveness

Exclusion criteria:

- Latent TB infection (only updated review)
- Systematic review (only used for reference searching)

EU/EEA = European Union, European Economic Area; OECD = Organisation for Economic Co-operation and Development; TB = Tuberculosis

**EU candidate countries = Albania, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, and Turkey*
*** OECD countries = Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States*

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Supplementary Material

Supplementary Material I: Original study protocol

Supplementary Material II. PICOS

Supplementary Material III. Search strategy

Supplementary Material IV. Evidence statements

Supplementary Material V. Data extraction forms

Supplementary Material VI. Quality Assessment

Supplementary Material VII. PRISMA checklist

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Effectiveness of service models and organisational structures supporting tuberculosis identification and management in hard-to-reach populations in countries of low and medium tuberculosis incidence: A systematic review

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Abstract

Objective To determine which service models and organisational structures are effective and cost-effective for delivering tuberculosis services to hard-to-reach populations.

Design Embase and MEDLINE (1990-20017) were searched in order to update and extend the 2011 systematic review commissioned by NICE, discussing interventions targeting service models and organisational structures for the identification and management of tuberculosis in hard-to-reach populations. The NICE and Cochrane Collaboration standards were followed.

Setting European Union, European Economic Area, European Union candidate countries and Organisation for Economic Co-operation and Development countries.

Participants Hard-to-reach populations, including migrants, homeless people, drug users, prisoners, sex workers, people living with HIV and children within vulnerable and hard-to-reach populations.

Primary and secondary outcome measures Effectiveness and cost-effectiveness of the interventions.

Results From the 19,720 citations found, five new studies were identified, in addition to the six discussed in the NICE review. Community health workers from the same migrant community, street teams and peers improved tuberculosis screening uptake by providing health education, promoting tuberculosis screening and organising contact tracing. Mobile tuberculosis clinics, specialised tuberculosis clinics and improved cooperation between health care services can be effective at identifying and treating active tuberculosis cases, and are likely to be cost-effective. No difference in treatment outcome was detected when directly observed therapy was delivered at a health clinic or at a convenient location in the community.

Conclusions Although evidence is limited due to the lack of high quality studies, interventions using peers and community health workers; mobile tuberculosis services, specialised tuberculosis clinics, and improved co-operation between health services can be effective to control tuberculosis in hard-to-reach populations. Future studies should evaluate the (cost-)effectiveness of interventions on TB identification and management in hard-to-reach populations and countries should be urged to publish the outcomes of their TB control systems.

Systematic review registration PROSPERO *CRD42015017865*.

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Strengths and limitations of this study

- PRISMA and Cochrane Collaboration reporting guidelines for systematic reviews were followed.
- The search was highly sensitive but we might have missed important information as many European countries do not publish their tuberculosis identification and management data in journals, our search focused on Embase and MEDLINE.
- We identified five studies and discuss the results together with the six studies identified by the NICE review to give the complete body of evidence.
- None of the included studies was of high quality and there was high heterogeneity across the studies prohibiting a meta-analysis.

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Introduction

Prevention and control of tuberculosis (TB) is based on early detection and diagnosis of TB followed by effective treatment. In 2015 there were an estimated 10.4 million incident TB cases worldwide, an estimated 4.3 million cases were either not diagnosed, or diagnosed but not reported to national TB programmes.[1] Trends for TB treatment are encouraging, with most notified TB cases completing their treatment successfully; although treatment success rates in some regions, such as the European region, were considerably below the WHO World Health Assembly target of 85%.[1]

In many countries with a low TB incidence (less than ten TB cases per 100,000 population),[2] TB prevails in the big cities where vulnerable and hard-to-reach (under-served) populations are concentrated.[3] These populations, such as people who are homeless (or have insecure accommodation), misuse drugs or are migrants, are at higher risk of contracting TB and are more likely unable or unwilling to seek medical care and comply with the long term TB treatment. Managing TB in those populations is therefore challenging, due to barriers caused by stigma, cultural barriers, poor access to health care services and low levels of accurate TB knowledge.[4,5-7] This therefore requires special efforts. Health care services need to be organised effectively to identify and diagnose TB cases, and to provide adequate treatment and support. This can be organised in different ways, e.g. mainly as hospital-based[8] or health centre-based;[9] including the public sector, private sector,[10] or civil society and other partners.[11] Sometimes, organisation of the services has proven ineffective in managing TB.[12]

The review question of this systematic review with a scoping component was: 'Which service models and organisational structures, including different types of healthcare workers and settings, are effective and cost-effective for delivering TB services to hard-to-reach populations in low- and medium-incidence countries?'

Findings of this review and the previously published review series [4,13] formed the base for the guidance document by the European Centre for Disease Prevention and Control (ECDC) on controlling TB in hard-to-reach and vulnerable populations.[14]

Methods

In 2011, the Matrix Knowledge Group published a review, commissioned by the National Institute for Health and Clinical Excellence (NICE), on effectiveness and cost-effectiveness of service models or structures, focussing on the type of health care worker and setting, to identify and manage TB in hard-to-reach populations. We updated and extended the NICE review,[15] using the same methodology but adjusting the focus by excluding latent TB infection and including additional hard-to-reach populations. The review was conducted following standards described by the Cochrane Collaboration[16] and NICE methods guidelines.[17] Results are reported according to PRISMA guidelines.[18] The review protocol was registered in advance in the database of prospectively registered systematic reviews in health and social care, PROSPERO (*CRD42015017865*).

Selection of studies and data management

The same search strategy as for the previous NICE review[15] and the previous published review by Heuvelings et al.[13] was used, searching Embase and MEDLINE through the Ovid platform. The search was expanded by including all European Union (EU)/European Economic Area (EEA) and EU candidate countries to the Organisation for Economic Co-operation and Development (OECD) countries (see **Box 1**).[15] Two hard-to-reach populations (people living with HIV and children within vulnerable and hard-to-reach populations), were added in addition to the hard-to-reach populations included by the NICE review (migrants including refugees, asylum seekers and the Roma population, homeless people including rough sleepers and shelter users, drug users, prisoners and sex workers).[15] The update of the search conducted for the NICE review[15] covered the period 1 January 2010 (overlapping the end of the search period of the NICE review[15] with a few months) to 24 February 2017. The search for the expanded geographical area and newly included hard-to-reach populations covered a time period from 1 January 1990 (beginning of the search period used in the NICE review[15]) to 24 February 2017.

Reference lists of relevant systematic reviews were scanned. No language restrictions were applied.

Studies focussing on the effectiveness and/or cost-effectiveness of interventions for service models and organisational structures supporting TB identification and management of hard-to-reach populations (see **Box 1**) were included.

Predefined interventions were using more convenient locations (like specialised TB centres, shelters for homeless people or drug users, needle exchange/methadone programme locations, port of arrival, schools or mobile clinics) and peers or health care workers with the same ethnic or cultural background; however, other interventions could also be included if they supported TB identification or management in hard-to-reach populations. TB identification tools, TB diagnostics, incentives, social support, directly observed therapy and treatment of co-morbidities are discussed in another review.[13] In this review we aim to identify the effectiveness of the type of health worker and setting, to identify and manage TB in hard to reach and vulnerable populations.

The comparator was defined during the review process; interventions were compared to a relevant comparator, for example usual care or no intervention, another intervention, or historical comparison.

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Outcomes were defined as any measure of TB identification and management (for example, number of people screened, screening coverage, proportion receiving treatment and treatment completion rate). Effectiveness was defined as an improvement in any measure of TB identification and/or management. Randomised and non-randomised studies were eligible for inclusion.

See **Supplementary Material I** for **the PROSPERO study protocol, Supplementary Material II for** PICOS (Population-Intervention-Comparator-Outcome-Study design) questions and **Supplementary Material III** for the complete search strategy and search results.

Data extraction, data items, and synthesis

Identified citations were entered into an EndNote database, and duplicates removed (EndNote X7.1, Thomson Reuters 2014). The inclusion criteria were piloted and refined using the first 25 citations. Double screening was conducted by one reviewer screening 100% of the citations (CCH) while another two reviewers screened 50% of the citations each (PFG, SGdV) for inclusion on title and abstract. Disagreement was resolved by discussion. Full text files of included citations were retrieved; irretrievable articles (not available after attempts online, from the university library or through contacting authors) were excluded. Two reviewers assessed full text records for inclusion (CCH, PFG). Disagreement was resolved by discussion. Agreement after screening on title and abstract was 99.6% with an inter-rater reliability (Cohen's kappa) of $\kappa = 0.985$.

Data extraction forms from the NICE review[15] were used to extract information on participant characteristics, settings, types of services/organisational structures, types of healthcare workers delivering the service, outcome measures, methods of analysis and results. For one study data extraction was conducted by two reviewers (CCH, PFG) independently. For the remaining studies, data extraction was conducted by one reviewer (CCH) and checked by a second (PFG); disagreement was resolved by discussion. In one case, the study author was contacted to verify data and obtain additional data.[19]

To facilitate comparability, data synthesis was structured in a similar way to that of the NICE review.[15] Studies were divided into those examining service models and organisational structures for TB identification (screening) and those examining service models and organisational structures for TB management (treatment and support) in hard-to-reach populations. Data were analysed narratively, and appropriateness of meta-analysis considered. Findings were reported as stated by the study authors.

Risk of bias in individual studies and overall strength of evidence

The modified NICE Quality Assessment Tools[17] (based on the Graphical Appraisal Tool for Epidemiological studies) were used to assess quality and risk of bias of included studies. This included an assessment of selection of study sample, minimisation of selection bias and contamination, controlling confounding, outcome measurements, analytical methods and risk of bias. Two reviewers (CCH, PFG) assessed one study independently; the remaining studies were assessed by one reviewer (CCH), and checked by a second reviewer (PFG). Any disagreement was resolved by discussion. Studies were given a quality rating based on the quality assessment: high quality [++], medium quality

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[+], or low quality [-]. The strength of the evidence was assessed and reported as described in the previous NICE review[15] (**Supplementary Material IV**).

Results

Of the 19,720 citations identified by the literature search five studies were included in this review (**Figure 1**).[11,19-22] These five studies are in addition to the six studies[23-28] included in the NICE review.[15] The results section in this paper focuses on the evidence of the five studies identified in our updated review. The evidence statements (presented in **Supplementary Material IV**) summarise evidence identified in terms of consistency, quality and applicability, combining evidence from the NICE review[15] and this update.

All five studies were conducted in the EU; two in the United Kingdom (UK),[19,22] one in Germany,[20] one in Portugal[11] and one in Spain.[21] Two studies focussed on homeless people,[19,20] one on homeless people and drug users,[22] one on drug users alone[11] and one on migrants.[21] Four studies[5,19-21] addressed the influence of the type of healthcare worker on TB identification and TB management and one study focussed on the influence of different settings on TB identification.[22] A variety of study designs were included; one study was a prospective cluster randomised controlled trial (RCT),[19] one was an economic evaluation using a compartmental model of treated and untreated active TB cases[22], and three studies were retrospective comparison studies.[11,20,21] Study characteristics of included studies are described in **Table 1**. The data extraction forms by study are presented in **Supplementary Material V**.

None of the included studies in this review had a low risk of bias, three studies[19,21,22] had a medium risk of bias, the other two studies[5,20] were assessed as having a high risk of bias (**Supplementary Material VI)**.

We did not perform a meta-analysis due to study heterogeneity. Results were synthesised narratively.[29]

Main outcomes for services structures and organisational models for TB identification among hard-to-reach populations, combined with the findings of the NICE review,[15] are summarised in **Table 2**. For full evidence statements, see **Supplementary Material IV**.

Three studies[19-21] compared the effect of the type of healthcare worker on TB identification.

In the UK, a cluster-randomised trial found that peer educators working together with shelter staff to encourage homeless people to participate in a TB screening programme using mobile X-ray units (MXU), did not improve screening uptake compared to encouragement by shelter staff only (respectively 40%, interquartile range [IQR] 25-61 versus 45%, IQR 33-55; adjusted risk ratio [aRR] 0.98, 95% confidence interval [95% CI] 0.80 to 1.20).[19] Control sites were not 'naïve' for peer intervention which could have caused contamination of the control sites and contributed to the negative finding.

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In Germany, introduction of TB education and promotion of voluntary chest X-ray (CXR) screening at least once every two years by community health workers (CHWs) improved screening uptake in homeless people and drug users. Annual screening coverage increased from 10.0% at the beginning of the study period (2002-2004) to 15.0% during the middle part of the study period (2004-2006), the last part of the study period had a 13.4% annual screening coverage (2005-2007). Screening once every two years increased screening coverage from 18.0% (2002-2004) to 26.4% (2004-2006). Coverage was 23.4% at the third and final study period (spanning 2005-2007).[20] The authors did not test for statistical significance, and denominator data (the number of homeless people and drug users in the study area) were estimated.

In Barcelona, Spain, contact tracing organised by CHWs coming from the same migrant community as the person diagnosed with TB, improved contact tracing among migrants to 66.2% (2003-2005) compared to 55.4% (2000-2002) in the period before the implementation of the intervention using CHWs (adjusted odds ratio [aOR] of an index case having their contacts screened before and after the intervention was 1.8, 95% CI 1.3 to 2.5, $p<0.001$).[21] Identification and tracing of at least one contact was taken as appropriate contact tracing, where all contacts at risk should be traced to detect and treat TB transmission early. The population characteristics varied, the age and country of origin was different between both periods. The importance of contact tracing is to identify cases early to reduce transmission, the authors did not report if any of the contacts traced had active TB.

Two studies[11,22] evaluated the effect of the type of healthcare worker and the setting on TB identification and TB management.

In Portugal, improved co-operation of 'key partners' (street teams, TB clinics, drug user support centres, local public health department and local hospital) for TB identification and management in drug users was evaluated in a before-and-after study. Representatives of all 'key partners' (authors' term) worked on improving policies, clinic screening procedures and co-operation. Key partners were trained in identifying drug users in their population; and offering health promotion, notification cards, free transport to the TB clinic, free medical and substance abuse care, directly observed therapy (DOT) for active TB cases, identification of non-compliant patients and the cause of non-compliance, and tailor-made strategies to improve compliance. This resulted in an increase of TB screening uptake; from 52 drug users being screened before the intervention (2001-2003 when there was no active screening policy) to 465 drug users screened thereafter (2005-2007). Of all people misusing drugs taking-up screening, the proportion without TB symptoms increased from 41.6% to 93.5% (OR = 21.76; 95% CI 13.03 – 36.33) indicating improved TB awareness and access to screening facilities for drug users. Of all drug users with active TB, the proportion identified by screening increased from 13·4% to 61·0% (OR 10·1; 95% CI: 4.44 – 23.0). Treatment default rates decreased from 35.4% to 10.2% (OR 0·.21, 95% CI 0.08-0.54), compared to the period before the intervention (2001-2003) when TB treatment was not compulsory and compliance was stimulated by TB education and providing information on the importance of treatment completion.[11] Although the absolute number of drug users screened increased, information on the screening coverage was not available as denominator

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data were not provided. Another limitation is that the results were not adjusted for confounding factors, baseline characteristics might have been different as the two cohorts were recruited over different time periods and participation was voluntary which may have led to selection bias.

In the United Kingdom, the effectiveness and cost-effectiveness of the 'Find and Treat' service (raising awareness of TB screening and providing a mobile TB screening and treatment service) for homeless people and drug users was evaluated and compared to people (with a history of homelessness, imprisonment, drug abuse or mental health problems) self-presenting to a London TB clinic receiving standard TB care at the clinic.[22] The authors estimated that 22.9% of the patients detected by the 'Find and Treat' service with the longest first symptom-to-detection time would not have self-presented plus 35.4% were asymptomatic at time of detection and would not have self-presented, only part of the asymptomatic patients would self-present to a TB clinic at a later stage when symptoms would have developed. The 'Find and Treat' service had a higher treatment completion rate (67.1% versus 56.8%), and a lower lost to follow-up rate (2.1% versus 17.2%) compared to the control group receiving standard TB care at a TB clinic. The authors concluded that the 'Find and Treat' service was cost-effective, when using the threshold used by NICE of £20,000 to £30,000/QALY gained, with an incremental cost ratio of £18,000 per QALY gained for the TB screening service and £4,100 per QALY gained for the TB management service. This study has a few limitations: firstly, it is a non-randomised study, secondly the 'Find and Treat' service identifies extremely hard-to-reach populations of which some would never self-present therefore the findings could be even better in less hard-to-reach populations, and thirdly the economical evaluation is based on a compartmental model that does not take secondary transmission and drug-resistance into account.

Discussion

To tackle TB and disrupt transmission in high-income, low TB incidence settings, improvement of TB care in hard-to-reach populations is of vital importance. In this updated review, five studies,[11,19-22] published between 1 January 2010 and 24 February 2017, evaluating effectiveness of services models and organisational structures supporting TB identification and management of hard-to-reach populations, were identified in addition to the six studies considering active TB[23-28] identified by the NICE review.[15] Only one study[22] evaluated cost-effectiveness. Although the evidence from two reviews is limited, it highlights those interventions that are likely to be effective and those that have no clear evidence of being effective (**Table 2**). For development of the ECDC guidance document,[14] a scientific panel compiled by ECDC carefully considered these findings. Their main suggestions for action were to involve CHWs or peers to improve TB screening uptake and TB treatment completion among homeless people[20] and drug users;[5,20,23] to use outreach teams to improve TB screening uptake and TB treatment completion among vulnerable populations;[22] and to strengthen relationships and good collaboration between health care workers, peers, communities, and patients to improve treatment outcome among vulnerable populations.[5,20,22,23] The updated systematic review provided evidence for all suggestions except for using peers to improve screening uptake. This is in contrast to an American

study[23] included in the original NICE review,[15] which showed that peers improved contact tracing and treatment adherence among drug users.

Strengths and limitations

PRISMA and Cochrane Collaboration reporting guidelines for systematic reviews were followed. Established screening protocols were used, including double screening, and the search was highly sensitive. The methodology from the previous NICE review[15] was followed, in order to connect this update and, so, describe the full body of relevant evidence. High quality evidence is lacking. Only one[23] study from the NICE review[15] was considered to be of high quality, all other studies had some risk of bias (five medium risk[19,21,22,24,26] and five high risk[11,20,25,27,28]). Therefore, only limited conclusions can be drawn. Most studies lacked identification and adjustment for confounding factors and the use of appropriate analytical methods. In addition, many studies were biased, particularly with regard to potential selection bias. A meta-analysis could not be performed, because of heterogeneity across the studies. Gaps in evidence exist; no studies focussing on children within vulnerable and hard-to-reach populations, or on people living with HIV or sex workers were identified. Only three studies provided economic data; one study identified by this review,[22] and two[25,27] by the NICE review.[15]

Our search focussed on publications in databases Embase and MEDLINE. Many European countries have strong organisational structures for TB identification and management, but these countries did not publish their data on these organisational structures in journals, which may have caused a publication bias. Comparing findings of the NICE review[15] with this review comes with some limitations. For the NICE review only 10% of the citations were double screened,[15] compared to 100% for this updated review, therefore studies conducted between 1990-2010 might have been missed. The NICE review focussed their recommendations on the population in the United Kingdom,[15] and this review focussed on populations in high-income, low TB incidence countries. Further methodology was identical.

The evidence identified by this review and the previous NICE review[15] along with evidence presented in a review series covering the barriers and facilitators of seeking TB care,[6] and the effectiveness of interventions for TB identification and management in hard-to-reach populations,[13] was used to develop the ECDC guidance on improving TB identification and management among hard-to-reach and vulnerable populations in Europe.[14] ECDC recommended that implementation of the interventions is context-specific; it depends on the setting, target population, resources available and health-care systems in place. Interventions focussing on one specific hard-to-reach population might not work in another hard-to-reach population, therefore, the interventions have to be adapted and re-assessed per target population.[14] Given the scope of this review, considering settings across Europe, findings presented here are potentially relevant to any low-incidence region, and are relevant to other institutions/governmental organisations seeking to improve service structures for TB identification and management among hard-to-reach populations.

Characteristics of different hard-to-reach populations and their TB epidemiology vary per country and setting. Challenges in identification and management of TB should be identified and targeted, tailored

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to the specific setting and hard-to-reach population. These TB interventions could be integrated within broader programmes targeting specific populations. A follow-up systematic review should include information from national public health services about their organisational structures for TB identification and management. National public health services are urged to regularly analyse their organisational structures for TB identification and management and publish this data.

Efforts to improve quality of research on service models and organisational structures should be made, even though it is often challenging to perform 'clean', unbiased, and un-confounded trials in hard-to-reach populations, as attrition rates are often high, and confounding factors are plentiful. This includes conducting (cluster) randomised controlled trials and before-and-after studies where appropriate, recruiting an adequate number of participants, using relevant control groups, and minimising selection bias. Standardised case definitions for hard-to-reach populations should be created. Feasibility, effectiveness, cost-effectiveness and impact of interventions should be evaluated. Mathematical economic models can be used to evaluate costs.[14]

Conclusions

Identification and management of TB in hard-to-reach populations is suboptimal.[2] Therefore, service models and organisational structures to identify and manage TB in hard-to-reach populations should be improved and evaluated regularly.

Our systematic review, in conjunction with the original NICE review[15] provides limited evidence, due to the lack of high quality studies, that interventions such as using peers and CHWs; mobile TB services, specialised TB clinics, screening, or active case finding in non-healthcare settings, as well as improved co-operation between key services can help to improve TB identification and management.

Further research should be undertaken to evaluate other effective and cost-effective ways to identify and manage TB in hard-to-reach populations and countries with good TB control systems are urged to evaluate their system and publish the data.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and all except for MPG and BS declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MPG reports grants from ECDC, for the conduct of part of the study. BS reports that NICE - her employing organisation - has published guidance in this area.

Authors' contribution

RS conducted the literature search. CCH, SGdV and PFG performed the study selection. CCH, and PFG collected the data, performed quality/risk of bias assessment and synthesised the data. CCH prepared the manuscript and supplementary files. MPG and MvdW supervised the whole process and contributed to the work. All authors were involved in interpretation of the data, and the writing of the manuscript. All authors contributed to, and endorsed the final version of the manuscript. MPG is guarantor.

Ethics

Ethics approval was not required for this systematic review.

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Statement of independence of researchers from funders

The funder of the study was involved in study design, data interpretation, and reporting. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Data extraction forms and quality assessment forms are available from **Supplementary files V** and **VI**.

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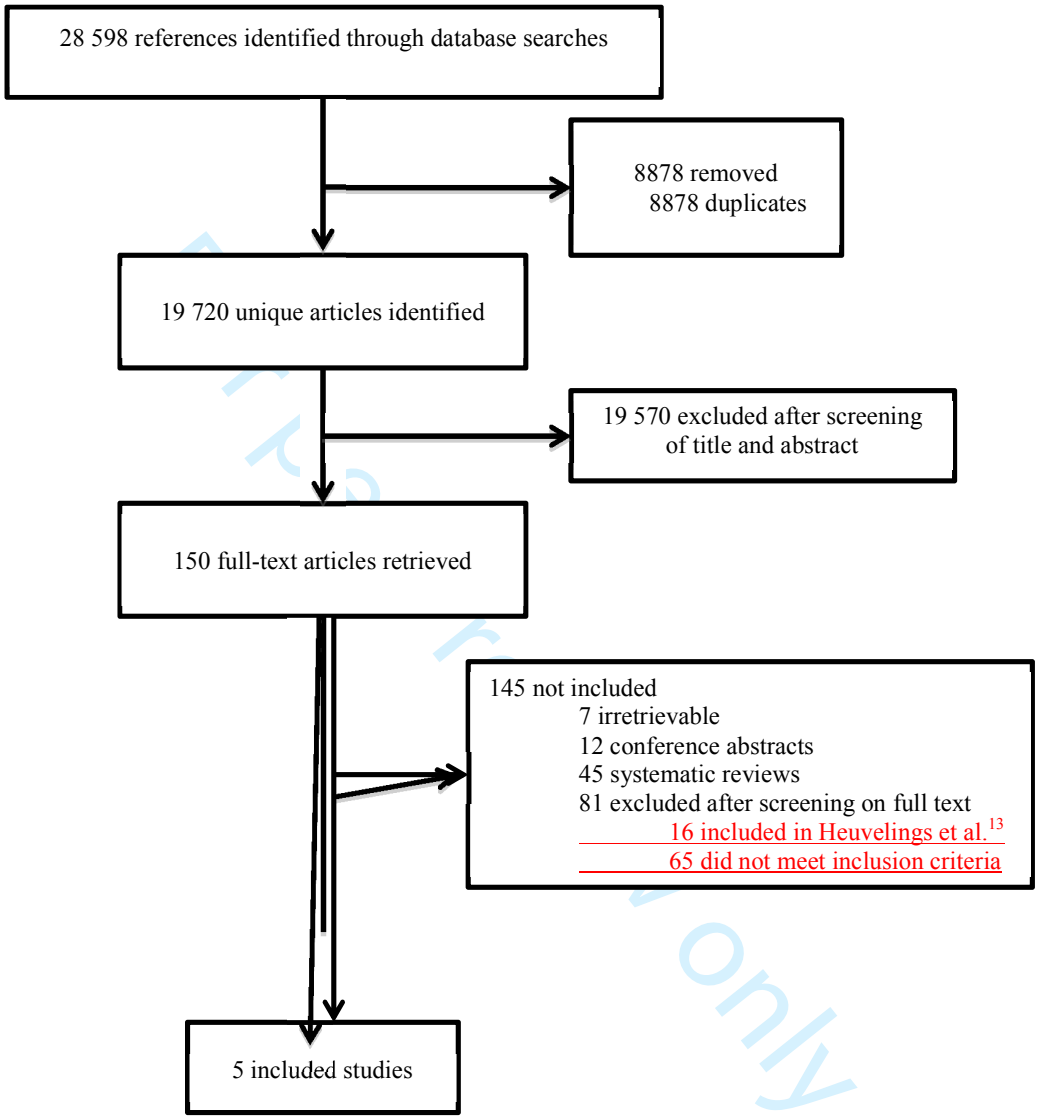
Figure 1. Study selection process



For the Organisation for Economic Co-operation and Development (OECD) countries and hard-to-reach populations discussed in the previous NICE review,[13] the study period covers 1 January 2010 to 24 February 2017
For the newly included European Union (EU)/European Economic Area/EU candidate countries, and the newly included hard-to-reach populations (people living with Human Immunodeficiency Virus (HIV) and children within vulnerable and hard-to-reach populations, the study period covers 1 January 1990 to 24 February 2017.

Table 1. Characteristics of studies applying different service models and organisational structures to improve TB identification and TB management

First Author (year) country	Population	Aims	Intervention	Comparator	Study design	Outcome measure	Quality score
TB identification (studies identified by this review)							
Jit et al. (2011)[22] United Kingdom	Homeless people and drug users	To assess the effectiveness and cost-effectiveness of the Find and Treat service for diagnosing and managing hard-to-reach individuals with active TB in London.	Period 2007-2010: Find and Treat service: - screening by MXU - peers raising awareness - treatment support	Passive case detection and standard treatment at a London TB clinic	Observational and cost-effectiveness study	Identified TB cases, treatment completion, lost to follow-up, incremental costs from healthcare taxpayer perspective	+
Duarte et al. (2011)[11] Portugal	Drug users	To evaluate the effect of an intervention with key partners (TB clinic, drug users support centres, shelters, street teams, public health department and hospital) delivering promotion of health-seeking behaviour, eliminating potential barriers for TB screening at a chest clinic and DOT, on identifying TB cases and treatment compliance.	Improved co-operation of key partners (2005-2007): - health education and screening promotion - improved screening procedures - implementation of DOT - free TB care and transport - providing medical and drug abuse treatment - active follow-up of non-compliant patients, the key partners worked together to reach the patient, identify the cause and organise suitable treatment strategies	Period before the intervention (2001-2003): - no active screening policy - referral to chest clinic after discharge from hospital - treatment not compulsory - information about disease and treatment given to improve compliance - psychosocial support - free TB treatment, transport and breakfast	Before-after study	Identified TB cases and treatment compliance	-
Goetsch et al. (2012)[20] Germany	Homeless people and drug users	To estimate the coverage of a low-threshold CXR screening programme for pulmonary TB among illicit drug users and homeless persons.	CHWs providing TB education and promoting voluntary CXR screening 1-2x/year	Comparing the beginning of the 5 year intervention period with the end (2002-2007)	Retrospective effectiveness study	Screening coverage	-
Ospina et al. (2012)[21] Spain	Migrants	To evaluate the effectiveness of an intervention with community health workers to improve contact tracing among migrants	CHWs active follow up of cases and contacts, including visits of the cases at home, accompanying at outpatient appointments, providing counselling and information on treatments (2003-2005)	Pre-intervention period (2000-2002)	Before-after study	Number of migrants that were included in contact tracing	+

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Aldridge et al. (2015)[19] United Kingdom	Homeless people	To compare TB screening uptake between current practice of encouraging homeless people by shelter staff and encouragement by shelter staff plus volunteer peer educators.	Encouragement of TB screening by peers in addition to shelter staff	Encouragement of TB screening by shelter staff only	Cluster randomised controlled trial	Screening uptake	+
TB identification (studies identified by the previous NICE review[15])							
El-Hamad et al. (2001)[24] Italy	Migrants	To compare the completion rates of screening procedures for TB infection among undocumented migrants at specialised TB units and non-specialised health clinics	TB screening at specialised TB clinic	TB screening at a general health service for migrants	Prospective cohort	Screening completion	+
Bothamley et al. (2002)[25] United Kingdom	Migrants and homeless people	To compare the yield and costs of TB screening in three settings: a new entrants' clinic within the port of arrival (POA) scheme; a large general practice; and centres for the homeless	TB screening at a general practice (GP)	TB screening at POA and at homeless centres	Cost analysis	Cost per person screened per case of TB prevented	-
Deruaz & Zellweger (2004)[28] Switzerland	Migrants, alcohol or drug users, homeless people and prisoners	Evaluation of first experience of the DOT programme for TB introduced in the Canton of Vaud in 1997	1. Full DOT 2. DOT delivered at TB clinic	1. Partial DOT (DOT only first 2 months of treatment) 2. DOT delivered at social outreach site	Before-after study	Adherence to treatment and outcome	-
Miller et al. (2006)[26] United States	Homeless people and prisoners	To evaluate and compare the efficiency of a non-state-law-mandated TB screening programme for homeless persons with a state-law-mandated TB screening programme for prisoners	Non-state-law-mandated TB screening programme for homeless persons	State-law-mandated TB screening programme for prisoners	Retrospective comparison of the cost and health impacts	TB cases averted and cost	+
Ricks (2008)[23] United States	Drug users	To compare the effectiveness of using peers versus 'standard' public health workers to coordinate TB treatment	Enhanced case management by peers	Limited case management by heath care professionals	Randomised controlled trial	Adherence to treatment	++

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Mor et al. (2008)[27] Israel	Migrants	To examine the effectiveness and cost-effectiveness of pre-migration screening and post-migration screening at POA	Pre-migration screening	Post-migration screening	Retrospective cohort analysis	Active TB cases, time between migration and diagnosis, cost-savings	-

List of Abbreviations

CHW = community health worker; CXR = chest X-ray; C = comparator group; DOT = direct observed treatment; GP = general practice; I = intervention group; IRIS = immune reconstitution inflammatory syndrome; IVDU = intravenous drug users; MXU = mobile X-ray unit; *n* = number of participants; QALYs = quality adjusted life years; POA = port-of-arrival; RCT = randomised controlled trial; TDM = therapeutic drug monitoring; TB = tuberculosis

Study quality: high quality [++], medium quality [+], or low quality [-]

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Table 2. Effectiveness of service models and organisational structures interventions to improve TB identification and TB management

Population	Intervention (I)	Comparator (C)	Studies (first author, year, country)	No. of participants I	No. of participants C	Comparison	Outcome	Risk of Bias
Homeless people Drug users	Health/TB education and promotion of screening by street teams, drug users support centres, shelters and CHWs	Beginning of the intervention when CHWs were just introduced No active screening policy	Goetsch et al. 2012 (Germany)[20] Duarte et al. 2011 (Portugal)[11]	465	125	Retrospective comparison over intervention period Retrospective before-after comparison	Improved annual TB screening uptake among homeless people and drug users (from 10.0% to 15.0% at the peak).[20] The percentage of all drug users with active TB identified by screening increased from 13.4% to 61.0% (OR 10.1 [95%CI 4·44-23·0]).[11]	High$_2$ High$_3$
Homeless people	TB education and promotion of screening by peers and shelter staff	TB education and promotion of screening by shelter staff only	Aldridge et al. 2015 (United Kingdom)[19]	1150	1192	Comparing randomised intervention cluster with comparator cluster	No difference in screening uptake (I = 40% [IQR 25-61] versus C = 45% [IQR 33-55], aRR= 0.98 [95%CI 0.80-1.20]).	Medium$_4$
Migrants	Pre-migration screening	Post-migration screening at POA	Mor et al. 2008, cited in the NICE review (Israel)[27]	162	105	Retrospective Intervention versus comparator comparison	Reduced the risk of developing TB in the new country and was cost-effective (0.28% of the pre-migration versus 0.32% of the post-migration screening migrants developed TB; RR 0.82 p<0.01)). The detection period was shorter as well (193 days versus 487 days between entry and diagnosis; OR=0.72 [95%CI 0.59-0.89] p=0.002).	High$_8$
Prisoners and homeless people	TB screening in a prison	TB screening at a homeless centre	Miller et al. 2006, cited in the NICE review (United States)[26]	22920	822	Retrospective comparison of two cohorts	No difference in screening uptake (94.7% in prison versus 95% in homeless centre p=0.179) but higher proportion of active TB cases were identified at the homeless centre (1.2% versus 0.03% at a prison setting, p<0.001)	Medium$_9$
Homeless people and migrants	Active case finding by symptom-based questionnaire at homeless centres	Active case finding by symptom-based questionnaire at POA	Bothamley et al. 2002, cited in the NICE review (United Kingdom)[25]	262	199	Cost analysis	Active case finding at POA was most cost-effective (costs per person screened for every case prevented at POA £10.00, at homeless centre £23.00).	High$_{10}$
Migrants	Active case finding at a specialised TB clinic using 2 visits	Active case finding at a general primary care clinic, with referral for CXR, using 3 visits	El-Hamad et al. 2001, cited in the NICE review (Italy)[24]	749	483	Prospective intervention versus comparator comparison	Improved screening completion among migrants (85.6% in TB clinic versus 71.4% at primary care clinic, p = not reported; OR=2.57 [95%CI 1.92-3.42]).	Medium$_5$

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Drug users Migrants	Contact tracing by peers or CHWs from the same migrant community	Peers versus other health care workers Normal practice before introducing CHWs	Ricks 2008, cited in the NICE review (United States)[23] Ospina et al. 2012 (Spain)[21]	48 388	46 572	RCT Before-after comparison	Improved contact tracing among drug users (75% by peers versus 47% by healthcare workers, p = 0.03)[23] and migrants (from 55.4% without CHWs to 66.2% with CHWs; aOR 1.8 [95%CI 1.3-2.5] *p*<0·001).[21]	Low Medium[1]
Drug users and homeless people	Mobile TB screening and treatment service at convenient location in the community	Passive case detection and management at a TB clinic	Jit et al. 2011 (United Kingdom)[22]	48	252	Prospective intervention versus comparator comparison plus economic evaluation	Improved TB identification among homeless people and drug users; particularly in asymptomatic patients (35.4% extra identified) and those that delay seeking health care (22.2% extra identified). Higher treatment completion rate (67.1% versus 56.8%) and lower lost to follow-up rate (2.1% versus 17.2%). Both parts of the service are cost-effective (screening = £18,000/QALY gained, treatment is £4,100/QALY gained)	Medium[6]
Drug users	Enhanced case management by peers	Limited case management by regular health care workers	Ricks 2008, cited in the NICE review (United States)[23]	48	46	RCT	Improved treatment completion in drug users (85% by peers versus 61% by health care workers, RR=2.68 [95%CI 1.24-5.82] p=0.01).	Low
Drug users	DOT and active follow-up of non-compliant patients by 'key partners'	Non-compulsory TB treatment and education about TB disease and treatment to improve compliance	Duarte et al. 2011 (Portugal)[11]	465	125	Retrospective before-after comparison	Reduced treatment default rates (from 35.4% to 10.2%; OR 0.21 [95%CI 0.08-0.54]).	High[2]
Migrants, drug users, homeless people and prisoners	DOT at a convenient location in the community	DOT at a health clinic	Deruaz & Zellweger 2004, cited in the NICE review (Switzerland) [28]	36	18	Retrospective before-after comparison	No significant difference in successful treatment outcome, treatment completion and cure rate (85.2% at convenient location versus 92.6% at health clinic, p=0.67)	High[7]

List of Abbreviations

aOR = adjusted odds ratio, aRR = adjusted risk ratio, C = comparator group, CHWs = community health workers, DOT = directly observed treatment, I = intervention group, IQR = interquartile range, OR = odds ratio, POA = port-of-arrival, RCT = randomised controlled trial, TB = tuberculosis, 95%CI = 95% confidence interval

Footnotes Risk of Bias:

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[1] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). Contact tracing of only one contact was enough to be called contact tracing, and the ultimate aim of contact tracing (increase cased detection and reduce transmission) was not analysed in this study.
[2] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). Denominator not given therefore unable to calculate screening coverage.
[3] = Risk of selection bias as participation was voluntary. Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods). No statistical test used to show statistical significance of the findings, an estimated number was used for the denominator.
[4] = Most comparator sites were not naïve for peer intervention, no individual information of the participants was collected, the characteristics between the two groups might have been significantly different.
[5] = Not adjusted for difference in baseline characteristics.
[6] = Study was designed to evaluate the cost-effectiveness, no statistical test used to evaluate statistical significant findings. The 'Find and Treat' service identifies extremely hard-to-reach populations that would never self-present, the findings would underestimate the benefit of the service. The economical evaluation is based on a compartmental model that does not take secondary transmission and drug-resistance into account,
[7] = Risk of bias due to difference in collecting treatment adherence outcome at the health clinic a nurse recorded treatment adherence at time of visit, in the social outreach group a health care worker was interviewed up to 6 months after treatment completion and was asked about the treatment adherence, risk of recall bias. Not recorded how many people per setting received 6 months of DOT (full DOT) and how many received 2 months of DOT and 4 months of self-treatment (partial DOT), what was another intervention in this study. Allocation to setting was based on needs of participants what might have caused bias.
[8] = Not adjusted for important confounding factors (intervention and comparator group were recruited over different time periods), pre-migration group had a shorter follow-up period than post-migration group what may have influenced the detection of number of TB cases in the pre-migration group.
[9] = Unclear if the differences in outcome was caused by the setting or by the different methods or to differences in TB prevalence in the different populations.
[10] = TB prevalence might be different in the different populations as the costs are calculated per active case detected this is a major issue, there were only 3 active TB cases detected, all in the POA group. The economic perspective used was not reported and the costs of identification were not discounted.

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Box 1: Inclusion/exclusion criteria for this review

Inclusion criteria:

- Discussing service models and organisational structures, different types of healthcare workers and settings for delivering TB services to hard-to-reach populations;
- Having been conducted in any of the EU/EEA countries (only updated review), the candidate countries* (only updated review) and the other OECD countries**
- Having been published in 2010 or later for the OECD countries**
- Having been published in 1990 or later for the EU/EEA countries and the EU candidate countries* not being one of the OECD countries (only updated review)
- Including data from any hard-to-reach population:
    - homeless people
    - people who abuse drugs or alcohol
    - sex workers
    - prisoners or people with a history of imprisonment
    - migrants, including vulnerable migrant populations such as asylum seekers, refugees and the Roma population
    - children within vulnerable and hard-to-reach populations (only updated review)
    - people living with HIV (only updated review)
- Present quantitative empirical data
- Being a (cost)-effectiveness study, or any other type of quantitative primary research, discussing (cost-)effectiveness

Exclusion criteria:

- Latent TB infection (only updated review)
- Systematic review (only used for reference searching)

EU/EEA = European Union, European Economic Area; OECD = Organisation for Economic Co-operation and Development; TB = Tuberculosis

**EU candidate countries = Albania, Montenegro, Serbia, the former Yugoslav Republic of Macedonia, and Turkey*
*** OECD countries = Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States*

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Supplementary Material

Supplementary Material I: Original study protocol

Supplementary Material II. PICOS

Supplementary Material III. Search strategy

Supplementary Material IV. Evidence statements

Supplementary Material V. Data extraction forms

Supplementary Material VI. Quality Assessment

Supplementary Material VII. PRISMA checklist

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PROSPERO International prospective register of systematic reviews

Evidence review of the effectiveness and cost effectiveness of service models or structures aiming to manage tuberculosis in hard-to-reach groups, including a qualitative description of these service models or structures

Charlotte Heuvelings, Sophia de Vries, Patrick Greve, Benjamin Jelle Visser, Saskia Janssen, Sabine Belard, Lianne Cremers, Rene Spijker, Martin Grobusch

Citation

Charlotte Heuvelings, Sophia de Vries, Patrick Greve, Benjamin Jelle Visser, Saskia Janssen, Sabine Belard, Lianne Cremers, Rene Spijker, Martin Grobusch. Evidence review of the effectiveness and cost effectiveness of service models or structures aiming to manage tuberculosis in hard-to-reach groups, including a qualitative description of these service models or structures. PROSPERO 2015:CRD42015017865 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015017865

Review question(s)

Which service models and service structures are most effective and cost-effective at supporting TB identification and management of hard-to-reach groups? How can these service models and organisational structures be qualitatively described?

The following service structures will be explored:

• Type of healthcare worker (any person who was used to deliver the intervention) used to identify and manage TB in hard-to-reach groups.

• Setting used to identify and manage TB in hard-to-reach groups.

Who is responsible for the commissioning and delivery of TB services?

What (if any) theories or conceptual models underpin the service models/organisational structures?

What specific individuals or populations are targeted by the interventions?

How does engagement in various service models/organisational structures differ by group/subgroup (in terms of hard-to-reach group, age, or gender)?

Searches

Data Bases Health:

• EMBASE

• MEDLINE

• MEDLINE In-Process

Search terms

1. ‘tuberculosis / TBC/ TB’ 2. ‘hard to reach groups /

population / people’ 3. ‘vulnerable groups / population / people / poor / poverty / overcrowded / excluded populations’

4. ‘homeless / hostels / shelters / poor / poverty’ 5. ‘drug* / substance* use* / abuse* / addict* / dependent / problem* /

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disorder*' 6. 'Alcohol* use* / abuse* / problem* / addict*' 7. 'sex-worker / prostitute* / transactional sex' 8. 'prison* / inmate / detaine* / detention / jail / imprisonment' 9. '*migrant* / illegal / Roma* / gips* / gyps* / international student / expat*' 10. 'child*' 11. 'HIV / AIDS co-infection' 12. 'RCT / *Controlled Trial' 13. 'Cohort stud*' 14. '*review*' 15. '*report*' 16. 'Case stud* / report*' 17. 'intervention*' 18. 'case finding (active or passive)' 19. 'case management / strategy / polic*' 20. 'prevention' 21. 'control' 22. 'management' 23. 'treat*' 24. 'Service model* / delivery / health care service* / urban health service*' 25. 'General practice / physician / GP / family practice / nurse lead' 26. 'Social work* / outreach / volunteer*' 27. 'Rehab* centre / pharmacy / ambulatory care / mobile clinic' 28. 'DOTS / directly observed therapy / adherence / patient compliance' 29. 'Telemedicine / telephone medicine' 30. 'Incentives / support' 31. 'Screening / counselling' 32. 'Chest X-ray/ radiography / CXR / diagnostic test / Mantoux / skin test / TST / GeneXpert / sputum smear / culture' 33. 'Health education / promotion' 34. 'Service provider' 35. 'Provider initiated / voluntary / patient initiated'

We will conduct five separate search strategies; the first two search strategies (one qualitative and one quantitative search) will be exactly the same searches as performed for the evidence reviews for the NICE guidelines. For these OECD countries, the searches will span from August 2010 till present (December 2014, with an update performed in the last contract month), without language barriers.

Types of study to be included
(cost-)effectiveness study, or any other type of quantitative/qualitative primary research, or a systematic

Condition or domain being studied
Tuberculosis public health interventions

Participants/ population
Hard to reach groups in European Union and OECD, like (illegal) migrants, sex workers, homeless, substance abusers, prisoners, HIV positive people and the children of these groups

Intervention(s), exposure(s)
The reviews aim to collect evidence on all areas of interventions and service models related to identification and management of TB in vulnerable and hard-to-reach populations, as defined in the systematic reviews by NICE.

- Improve coverage and uptake of screening and active case finding by:

• using more convenient locations (like specialised TB clinic, centres for the homeless, large general practise, port of arrival, schools, syringe exchange programmes, mobile clinic)

• using peers or staff from the same hard to reach group (as case managers or health advisors)

• using small monetary incentives or food vouchers

• identifying more members of hard to reach groups

- IPT combined with methadone treatment for drug users

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- Directly Observed Therapy (DOT(S)) by peers and in more convenient locations

- Family based DOT(S) programme

- Legal detention to manage active TB

- Social care support

- Enhanced case management

- Directly Observed Preventive Therapy (DOPT) plus incentives

Additionally, we aim at considering the following additional interventions:

- General interventions to improve the situation for the vulnerable and socially disadvantaged groups, e.g. provision of housing, nutritional programmes, addressing challenges related to immigration from high-TB burden countries, addressing inequalities and socioeconomic deprivation

- Case finding, contact tracing and screening programmes, by classic or innovative interventions for active case finding to reduce delays in case detection and limit further transmission

- Case holding and treatment interventions to maximise treatment initiation, adherence and completion

- Use of peer support, incentives, and other means to increase effectiveness of any interventions aimed at case finding, case holding or case management

- The existence of programs aimed collaborations with, or interventions aimed at, alternative, traditional, and / or spiritual medicine in TB treatment. This could be a problem that could be an obstacle in the control in TB in mainly immigrants and asylum seekers originating from non-western countries

- Programmes aimed at detection of patients from vulnerable or hard-to-reach populations who were lost to follow-up will be included as well.

- Treat comorbidities including HIV, diabetes, hepatitis, substance use disorders

- Continuity of care in the public sector for prisoners released from prison

- Improve living conditions and nutrition for prisoners

- General policies, health system organisation and structure of services that are aiming at enhancing access of care of specific targeted vulnerable groups, to make health care (including TB services) less hard to reach for these individuals

As this is a follow-up on the review done by NICE the following inclusion criteria will be used:

• Have a focus on TB services of any kind;

• Are conducted in any of the EU/EEA countries, the 5 candidate countries and the other OECD countries

• Are published in 2010 or later for the OECD countries;

• Are published in 1990 or later for the EU/EEA countries and the 5 candidate countries;

• Include data from any hard-to-reach group

• Present qualitative and/or quantitative empirical data;

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• Discuss an intervention relating to one of the following: identifying TB cases; managing TB cases; design of service models, and:

• is a (cost)-effectiveness study, or any other type of quantitative primary research, or a systematic review.

Studies focussing on the detection and management of latent TB infection are not in the scope of this review.

Comparator(s)/ control

Not relevant

Context

The research needs to take place in an EU or OECD country and focus on any of the earlier mentioned hard to reach groups

Outcome(s)

Primary outcomes

The most (cost-)effective service models and service structures at supporting TB identification and management of hard-to-reach groups

Secondary outcomes

Who are responsible for putting these service structures in place and organise them.

Data extraction, (selection and coding)

Following PRISMA guidelines, study selection will be performed by two separate review authors. Three authors will screen titles and abstracts independently in parallel for matching our research objectives. Consequently, full versions of potentially relevant articles will be retrieved to assess eligibility. All full-text articles will be double screened. Data will be collected from each publication and captured using the data extraction forms, according to the type of study. Data will be extracted from text, tables and figures. The data extraction forms will be completed independently by two review authors for a randomly selected sample of 10% of records. For the other records, the tool will be completed by one reviewer and checked by another, with any disagreements resolved by discussion or consultation of a senior study investigator.

Risk of bias (quality) assessment

In concordance with PRISMA guidelines and the NICE guidance document, methodological quality and risk of bias will be assessed separately for each eligible study. Two review authors will pilot-test the tool independently on five randomly selected studies. Quality assessments will be performed independently by two review authors for 10% of the included studies, for the remaining 90% of the records the tool will be completed by one reviewer and checked by another, disagreements will be resolved by discussion or consulting the third review author.

Strategy for data synthesis

We will decide to perform a meta-analysis according to the quality assessment scores and risk of bias assessments. If studies do not support meta-analysis, data will be synthesized narratively. Overall strength of the evidence will be assessed and reported in an additional file. Strength analysis will be performed by the reviewer who performed the data extraction and quality assessment for the respective studies.

Analysis of subgroups or subsets

Every subgroup will be analysed separately (see previous answer)

Contact details for further information

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Details of any existing review of the same topic by the same authors
Not by the same authors but this review is a follow up of:

Identifying and managing tuberculosis among hard-to-reach groups. Public health guidance, PH37 - Issued:

March 2012. NICE – National Institute for Health and Care Excellence. Available at: http://guidance.nice.org.uk/PH37

Anticipated or actual start date
15 December 2014

Anticipated completion date
01 June 2015

Funding sources/sponsors
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Conflicts of interest
None known

Language
English

Country
Netherlands, Sweden

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Cost-Benefit Analysis; Disease Management; Humans; Tuberculosis

Stage of review

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NHS
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Completed and published

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11 April 2017

Details of final report/publication(s)
Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review

Heuvelings, Charlotte C et al.

The Lancet Infectious Diseases , 2017, http://dx.doi.org/10.1016/S1473-3099(16)30532-1.
http://thelancet.com/journals/laninf/article/PIIS1473-3099(16)30532-1/fulltext

DOI
10.15124/CRD42015017865

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

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International prospective register of systematic reviews
The information in this record has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.

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Supplementary Material II: PICOS (Population – Intervention – Comparator – Outcome – Study design)

1. Review question

Which service models and organisational structures, including different types of healthcare workers and settings, are effective and cost-effective for delivering TB services to hard-to-reach populations?

2. PICOS

Population

Hard-to-reach groups in low incidence countries, like:

- homeless people including rough sleepers and shelter users
- people who abuse drugs or alcohol
- sex workers
- prisoners or people with a history of imprisonment
- migrants, including vulnerable migrant populations such as asylum seekers, refugees and the Roma population
- children within vulnerable and hard-to-reach populations
- people living with HIV

Studies focusing on hard-to-reach populations from Organisation for Economic Co-operation and Development (OECD) countries, European Union, European Economic Area (EU/EEA) countries and the EU candidate countries were included.

EU/EEA and candidate countries	**OECD countries**
1. Albania	1. Australia
2. Austria	2. Austria
3. Belgium	3. Belgium
4. Bulgaria	4. Canada
5. Croatia	5. Chile
6. Cyprus	6. Czech Republic
7. Czech Republic	7. Denmark
8. Denmark	8. Estonia
9. Estonia	9. Finland
10. Finland	10. France
11. France	11. Germany
12. Germany	12. Greece
13. Greece	13. Hungary
14. Hungary	14. Iceland
15. Iceland	15. Ireland
16. Ireland	16. Israel
17. Italy	17. Italy

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18. Latvia
19. Liechtenstein
20. Lithuania
21. Luxembourg
22. Malta
23. Montenegro
24. Netherlands
25. Norway
26. Poland
27. Portugal
28. Romania
29. Serbia
30. Slovakia
31. Slovenia
32. Spain
33. Sweden
34. The former Yugoslav Republic of Macedonia
35. Turkey
36. United Kingdom

18. Japan
19. Korea
20 Luxembourg
21. Mexico
22. Netherlands
23. New Zealand
24. Norway
25. Poland
26. Portugal
27. Slovak Republic
28. Slovenia
29. Spain
30. Sweden
31. Switzerland
32. Turkey
33. United Kingdom
34. United States

Studies that did not specifically look at any of these target populations or were conducted in a different geographical area were excluded.

Intervention

This review aimed to collect evidence on all areas of interventions targeting service structures and service models for the identification and management of TB in vulnerable and hard-to-reach populations. These interventions can cover activities to improve TB services for screening, active case finding or TB management. Predefined interventions included in the protocol were:

- Using different locations like:
    - Hospitals
    - Specialised TB clinics
    - Shelters for homeless people
    - Needle/syringe exchange programmes
    - Locations that combine care: providing treatment for drug addiction, medical care, HIV care
    - Large general practises
    - Port of arrival
    - Schools
    - Mobile clinics
    - Prisons
- Using different type of health care workers like:

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- Doctors
- Nurses
- Community health workers
- Peers
- People from the same background

- Others

- Family based DOTS programs
- Social care support and general interventions
  - Provision of housing
  - Nutritional programmes
  - Addressing challenges related to immigration from high-TB burden countries
  - Addressing inequalities and socioeconomic deprivation
- Collaboration with alternative, traditional, and / or spiritual medicine

Comparator

Not relevant.

The comparator was re-defined during the review process into:

Standard care.

Outcome

The outcome measures were quantitative outcomes focusing on the effectiveness and/or cost-effectiveness of service structures and service models aiming to identify and manage TB in hard-to-reach populations in low incidence countries, including a qualitative description of these interventions.

Study design

Randomised controlled trials (RCTs) focusing on service models and organisational structures on the selected hard-to-reach populations were included. Since it was very likely that few RCTs would be identified, we also included non-randomised studies like, but not exclusively, case-control studies, cohort studies, cross-sectional studies and observational studies. Quantitative and qualitative studies were included. Systematic reviews were included for reference checking only.

3. Further notes on PICOS

For this systematic review of interventions with a scoping component, a very broad and sensitive search was conducted to cover a wide range of interventions. Predefined interventions were included in our registered protocol but the list of interventions was not exclusive and interventions were added to the list during the review process. Supplementary Material I reflects the registered protocol. Changes made during the implementation of the systematic review protocol are stated at the end of each section.

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Supplementary Material III: Search strategies

The previous NICE review[1] on the same topic was used as a framework for the search strategy and extended to the non-Organisation for Economic Co-operation and Development (OECD), countries of the European Union and European Economic Area and to the two newly included hard-to-reach groups (people living with HIV co-infected with TB and children within vulnerable and hard-to-reach populations). The search for the NICE review[1] was subtracted from our search to prevent double screening of records. The search was conducted by René Spijker, clinical librarian at the Academic Medical Center in Amsterdam, the Netherlands. All studies identified by the search were imported to an Endnote database. The original search was done on the 10th of December 2014 and updated on the 10th of April 2015 and 24th of February 2017.

The following two databases were used for the search:

- MEDLINE(R) In-Process & Other Non-Indexed Citations (OvidSP)
- Embase Classic + Embase

Database	**Hits**
Medline + Medline In-Process	12,519
Embase	16,079
Total	**19,720**

References:

1. Rizzo M, Martin A, Jamal F, et al. Evidence review on the effectiveness and cost-effectiveness of service models or structures to manage tuberculosis in hard-to-reach groups. London: Matrix evidence/National Institute for Health and Clinical Excellence 2011. https://www.nice.org.uk/guidance/PH37/ documents/review-4-evidence-review-on-the-effectiveness-and-cost-effectiveness-of-service-models-or-structures-to-manage-tuberculosis-in-hardtoreach-groups-2 (last assessed March 2017).

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1. Search in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Hits: 12,519

1	exp *tuberculosis/ or (tuberculosis or tb).ti,ab.
2	((hard$ adj2 reach) or (hard$ adj2 locate) or (hard$ adj2 find) or (hard$ adj2 treat) or (difficult adj2 locate) or (difficult adj2 engage) or social$ exclu$ or social inequalit$ or (difficult$ adj2 reach) or (difficult$ adj2 find) or (difficult$ adj2 treat) or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*) or (muslim* or islam* or mosque* or imam*)).ti,ab. or exp *Jew/ or (jew* or judaism* or synagogue*).ti,ab. or exp *religion/ or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*).ti,ab. or (jew* or judaism* or synagogue*).ti,ab. or (sikh* or hindu* or buddhis* or temple*).ti,ab. or ((religion* or religious* or faith*) and (people* or person* or group* or population or neighbour* or neighbor* or patient* or communit*)).ti,ab.
3	((geograph$ or transport$ or physical) and barrier$).ti,ab.
4	((low$ or poor$ or negative) and (quality adj2 life)).ti,ab.
5	((vulnerable or disadvantaged or at risk or high risk or low socioeconomic status or neglect$ or affected or marginal$ or forgotten or non-associative or unengaged or hidden or excluded or transient or inaccessible or underserved or stigma$ or inequitable) and (people or population$ or communit$ or neighbourhood$1 or neighborhood$1 or group$ or area$1 or demograph$ or patient$ or social$)).ti,ab. or exp *vulnerable population/
6	*poverty/
7	(refuser$1 or nonuser$1 or non-user$1 or non user$1 or discriminat$ or shame or prejud$ or racism or racial discriminat$).ti,ab.
8	*social support/ or exp *social status/ or *social stigma/ or exp *social isolation/ or exp *"quality of life"/ or exp *prejudice/ or exp *socioeconomics/
9	prisoner$1.ti,ab.
10	(recent$ adj2 release$ adj2 (inmate$ or prison$ or detainee$ or felon$ or offender$ or convict$ or custod$ or detention or incarcerat$ or correctional or jail$ or penitentiar$)).ti,ab.
11	((prison$ or penal or penitentiar$ or correctional facilit$ or jail$ or detention centre$ or detention center$) and (guard$1 or population or inmate$ or system$ or remand or detainee$ or felon$ or offender$1 or convict$ or abscond$)).ti,ab.
12	(parole or probation).ti,ab.
13	exp *prisoner/
14	((custodial adj (care or sentence)) or (incarceration or incarcerated or imprisonment)).ti,ab.
15	(immobile or (disabled and (house bound or home bound)) or ((house or home) adj3 bound)).ti,ab. or exp *homebound patient/
16	((hous$ and (quality or damp$ or standard$ or afford$ or condition$ or dilapidat$)) or ((emergency or temporary or inadequate or poor$ or overcrowd$ or over-crowd$ or over-subscribed) and (hous$ or accommodation or shelter$ or hostel$ or dwelling$))).ti,ab. or exp *housing/
17	(rough sleep$ or runaway$1 or ((homeless$ or street or destitut$) and (population or person$1 or people or group$ or individual$1 or shelter$ or hostel$ or accommodation$1))).ti,ab. or exp *homelessness/
18	((drug$ or substance) and (illegal or misus$ or abuse or intravenous or IV or problem use$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)).ti,ab. or exp *addiction/
19	((alcohol$ and (misus$ or abuse or problem$ use$ or problem drink$ or illicit use$ or addict$ or dependen$ or delinquency)) or alcoholic$1).ti,ab.
20	(prostitution or sex work$ or transactional sex$ or prostitute$1).ti,ab. or Prostitution/
21	(poverty or deprivation or financial hardship$).ti,ab.
22	((low-income or low income or low pay or low paid or poor or deprived or debt$ or arrear$) and (people or person$1 or population$1 or communit$ or group$ or social group$ or neighbourhood$1 or neighborhood$1 or famil$)).ti,ab. or exp *lowest income group/
23	*poverty/
24	(low$ and social class$).ti,ab.

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25	(traveller$1 or gypsies or gypsy or Romany or roma).ti,ab. or exp *"Romani (people)"/
26	(mental$ and (health or ill or illness)).ti,ab. or *mental patient/ or exp *mental health/
27	(health care worker$1 or (health care adj2 service provi$) or (health-care adj2 provi$) or (((community adj1 leader$) or (community adj1 (Manag$ or advocat$ or champion$))) and (engag$ or involv$))).ti,ab.
28	(complex adj2 (patient$ or Need$)).ti,ab.
29	(outreach adj2 worker$1).ti,ab. or exp *health auxiliary/
30	(support adj2 worker$1).ti,ab.
31	(case adj2 worker$1).ti,ab.
32	(social adj2 worker$1).ti,ab.
33	social care professional$1.ti,ab.
34	((social care adj2 service provi$) or (social-care adj2 provi$)).ti,ab.
35	(((language$ or communicat$) and (barrier$ or understand$ or strateg$ or proficien$)) or translat$ or interpret$ or (cultur$ and competen$)).ti,ab. or *language ability/
36	(immigrant$ or migrant$ or asylum or refugee$ or undocumented or foreign born or (born adj overseas) or (displaced and (people or person$1))).ti,ab. or exp *refugee/
37	exp *migrant/
38	*immigration/
39	or/2-38
40	Intervention$.ti,ab. or exp *crisis intervention/
41	((early or primary) adj2 Intervention$).ti,ab.
42	((person$ or individual or local$ or community or cultural or structural or supported or indicated or target$ or multi?component or comprehensive or pilot or media) and Intervention$).ti,ab.
43	((midstream or mid-stream) and intervention$).ti,ab.
44	(Identify$ or find or finding or locat$ or trac$ or contact$ or discover$ or detect or recruit$ or attract$).ti,ab.
45	(case finding or ((active or passive) adj3 case finding)).ti,ab.
46	((program$ or scheme$1 or service$1 or campaign$ or mobili?ation or strateg$ or measure or policy or policies) and (tuberculosis or tb)).ti,ab.
47	((case adj3 management) or case-managed).ti,ab. or *case management/ or *patient care planning/ or *case management/ or exp *health care management/
48	(case adj3 manag$ adj3 strategy).ti,ab. or continuity of * patient care/
49	((treat$ or diagnosis) and management).ti,ab.
50	((active or passive) and (Case adj3 Management)).ti,ab.
51	(risk assess$ or risk profile or risk Indicator or care plan$).ti,ab.
52	(service and (model$ or deliver$)).ti,ab. or delivery of * health care/ or *health service/
53	((primary adj3 healthcare) or ((primary adj3 health$) or care)).ti,ab. or exp *primary health care/
54	(nurse or ((general or family) adj3 (practice$ or practitioner$ or physicians$ or doctor$))).ti,ab. or exp *nurse/ or (exp *tuberculosis/ or (tuberculosis or tb).ti,ab.) or exp *general practice/
55	((health or extension or multi-disciplinary or multidisciplinary) and (professional$ or personal$ or practitioner or worker$ or partner$ or promot$ or provider or care team or care provider or unit or casework$ or (case adj2 work$))).ti,ab. or *health care personnel/ or exp *nursing assistant/
56	(social adj2 (work$ or Support$ or Outreach)).ti,ab. or *social work/ or *social support/
57	(volunteer$ or voluntary or charit$ or third sector).ti,ab. or *voluntary worker/ or exp *health care organization/
58	(health adj1 (center$1 or centre$1 or facilit$ or service$ or clinic$1 or hospital$1 or program$1)).ti,ab. or *public health/ or *residential care/
59	((day adj2 (care or hospital$ or patient$)) or workshop$).ti,ab. or *day care/
60	rehab$.ti,ab. or *rehabilitation center/
61	((dedicated or permanent or rapid access or fixed or TB or tuberculosis) and (clinic$1 or centre$1 or center$1 or program$)).ti,ab.
62	(((drug adj2 dependency) or substance abuse or HIV) and (unit$ or clinic$1 or centre$1 or center$1 or program$) and (tuberculosis or tb)).ti,ab.
63	(pharmac$ or dispensary).ti,ab. or *pharmacy/

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64	(communit$ or (support$ adj2 communit$)).ti,ab. or *community care/ or *health auxiliary/ or *public relations/ or *community hospital/ or *community health nursing/
65	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
66	(ambulatory adj2 care).ti,ab. or exp *ambulatory care/
67	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (health adj3 (care or work$ or practitioner$ or professional$ or service$ or center$1 or centre$1 or unit$1 or program$))).ti,ab. or *preventive health service/
68	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (nurs$ or doctor$)).ti,ab.
69	((out adj3 hours) or (after adj3 hours) or telephone or telemedicine).ti,ab. or after-hours care/ or exp *telehealth/ or *emergency care/ or *health care delivery/
70	((walk-in or walkin or walk in) adj2 (center$1 or centre$1 or service or program$ or Clinic$1 or Session or Assesment$1)).ti,ab.
71	(drop$ adj1 in adj2 (center$1 or centre$1 or service or program$ or clinic$1 or session or meeting or assesment$1)).ti,ab.
72	(((health or home$ or house$) and (call$ or visit$)) or (home-care or home-based or (support$ adj1 hous$))).ti,ab. or Home Health Aides/ or *health auxiliary/ or exp *home care/
73	((early adj2 discharge) or (recent$ adj2 discharged) or (out adj2 patient)).ti,ab. or *patient care/ or *outpatient department/
74	(counselling or counseling or counsellor or counselor or (integrated counselling adj1 testing centre$1) or (integrated counselling adj1 testing center$1) or ICTC).ti,ab. or *counseling/ or *directive counseling/
75	((help adj2 group$) or (self adj2 help) or support$ or (peer adj2 peer)).ti,ab. or *self help/
76	(collaborat$ or shared or (integrated adj1 care$) or ICP or network$ or co-locat$ or (one adj1 stop)).ti,ab. or *integrated health care system/
77	((health adj2 education) or (skill adj2 mix) or (role adj2 develop$) or leadership or ((interdisciplinary or inter-team or Professional or team) adj2 communicate$)).ti,ab. or exp *health education/ or exp *interdisciplinary communication/ or *leadership/ or *doctor patient relation/ or *nurse patient relationship/ or patient relationship*.ti,ab.
78	((outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium) and (tuberculosis or tb)).ti,ab.
79	((outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium) and (tuberculosis or tb)).ti,ab.
80	or/40-79
81	test$.ti,ab.
82	(examination$1 or assessment$1 or identification or assay$ or detection).ti,ab.
83	diagnosi$.ti,ab. or *diagnostic test/
84	((chest adj2 x?ray) or chest radiograph or MXU).ti,ab. or *thorax radiography/
85	(screen$ or (new$ adj1 screen$)).ti,ab.
86	(monitor$ or sampling).ti,ab.
87	((target$ or focus$ or community or population or individual$ or person$ or opportunistic or coerc$ or voluntary or initiated) and (test$ or diagnosis or screen$ or assay$ or detection)).ti,ab.
88	PIT.ti,ab.
89	provider initiated test$.ti,ab.
90	((rapid or prompt or quick$ or earl$ or (point adj2 care)) and (test$ or screen$ or diagnosi$ or assay$ or detection)).ti,ab.
91	((provider or anonymous or accurate or support$ or incentiv$ or counsel$) and (test$ or diagnosis or screen$ or assay$)).ti,ab. or *anonymous testing/
92	(test$ adj2 (center$1 or centre$1 or unit$1 or setting)).ti,ab.
93	or/81-92
94	(acceptability or acceptable or attend$ or access$ or availab$ or non-attend$ or increas$ or promot$ or opt$ or particip$ or adhere$ or involvement or uptake or take-up or utiliz$ or utilis$ or refus$ or referr$ or self-referr$ or self-report$ or barrier$ or decreas$ or isolation or interven$ or aware$ or opportunit$ or advice or information or incentiv$ or recruit$ or

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	find or finding or compliance or comply or retain or retention or provision or encour$ or usage).ti,ab.
95	(socio sanitary support or reimburs$ or (social adj2 support) or ((cash or financial or money or monetary or economic or voucher or credit or drug$1 or methadone or telephone) adj2 (benefit$ or support or incentive or assist$ or credit))).ti,ab.
96	(((lifestyle or behavio?r) adj2 (therapy or modif$ or chang$ or adapt$ or adopt$)) and (tuberculosis or tb)).ti,ab. or *social marketing/
97	*marketing/
98	*attitude to health/
99	*health care delivery/
100	*access to information/
101	*confidentiality/
102	*Health education/
103	*health promotion/
104	*patient compliance/
105	*motivation/
106	Stigma.ti,ab.
107	*prevalence/
108	*patient participation/
109	*patient attitude/ or *refusal to participate/ or *treatment refusal/
110	or/94-109
111	treat$.ti,ab. or Treatment Outcome/
112	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or *directly observed therapy/
113	(disease management or (treat$ and (management or control))).ti,ab.
114	((adherence or compli$ or non-compli$ or default$ or finish$ or Retention or attrition or (drop adj1 out) or disappear$ or abscond$) and treat$).ti,ab. or exp *patient compliance/
115	((referr$ or self-referr$ or (self adj diagnos$)) and treat$).ti,ab.
116	((suitab$ or eligib$) and treat$).ti,ab.
117	((follow adj1 up) or discharge).ti,ab. or *follow up/
118	((positive or negative) and test).ti,ab.
119	((interrupt$ or relapse$ or stop$ or cessation or with?ld$ or avoidance or (lost adj2 follow)) and treat$).ti,ab. or *treatment withdrawal/
120	((medicine$1 or drug or treat$) and (regimen or adherence)).ti,ab. or exp *self care/
121	(treat$ and (appointment$ or Schedule$)).ti,ab. or *patient scheduling/
122	((care adj2 seeking) and pathway$).ti,ab.
123	((case adj3 management) or case-managed).ti,ab. or Case Management/ or *patient care planning/ or *health insurance/
124	(case adj3 manag$ adj3 strategy).ti,ab. or continuity.mp. or *patient care/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
125	((case or treat$ or diagnosis) and management).ti,ab.
126	((risk assessment or care plan$) and (case adj3 management)).ti,ab.
127	((active or passive) and (case adj3 management)).ti,ab.
128	or/111-127
129	1 and 39 and (80 or (93 and (110 or 128)))
130	limit 129 to yr="1990 -Current"
131	limit 130 to "english language"
132	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
133	131 not 132
134	limit 133 to yr="1990 - 2010"
135	(albania or bulgaria or cyprus or croatia or latvia or lithuania or luxembourg or malta or montenegro or romania or serbia or yugoslav or turkey).ti,ab,hw,in.
136	1 and 135 and (80 or (93 and (110 or 128)))
137	limit 136 to yr="1990 -Current"
138	137 not 132

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139	138 not 130
140	133 not 134
141	139 or 140

2. Search in Embase Classic + Embase 1947 to 2014 December 2008
Ovid
Hits: 16,079

1	**exp *tuberculosis/ or (tuberculosis or tb).ti,ab.**
2	((hard$ adj2 reach) or (hard$ adj2 locate) or (hard$ adj2 find) or (hard$ adj2 treat) or (difficult adj2 locate) or (difficult adj2 engage) or social$ exclu$ or social inequalit$ or (difficult$ adj2 reach) or (difficult$ adj2 find) or (difficult$ adj2 treat) or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*) or (muslim* or islam* or mosque* or imam*)).ti,ab. or exp *Jew/ or (jew* or judaism* or synagogue*).ti,ab. or exp *religion/ or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*).ti,ab. or (jew* or judaism* or synagogue*).ti,ab. or (sikh* or hindu* or buddhis* or temple*).ti,ab. or ((religion* or religious* or faith*) and (people* or person* or group* or population or neighbour* or neighbor* or patient* or communit*)).ti,ab.
3	((geograph$ or transport$ or physical) and barrier$).ti,ab.
4	((low$ or poor$ or negative) and (quality adj2 life)).ti,ab.
5	((vulnerable or disadvantaged or at risk or high risk or low socioeconomic status or neglect$ or affected or marginal$ or forgotten or non-associative or unengaged or hidden or excluded or transient or inaccessible or underserved or stigma$ or inequitable) and (people or population$ or communit$ or neighbourhood$1 or neighborhood$1 or group$ or area$1 or demograph$ or patient$ or social$)).ti,ab. or exp *vulnerable population/
6	*poverty/
7	(refuser$1 or nonuser$1 or non-user$1 or non user$1 or discriminat$ or shame or prejud$ or racism or racial discriminat$).ti,ab.
8	*social support/ or exp *social status/ or *social stigma/ or exp *social isolation/ or exp *"quality of life"/ or exp *prejudice/ or exp *socioeconomics/
9	prisoner$1.ti,ab.
10	(recent$ adj2 release$ adj2 (inmate$ or prison$ or detainee$ or felon$ or offender$ or convict$ or custod$ or detention or incarcerat$ or correctional or jail$ or penitentiar$)).ti,ab.
11	((prison$ or penal or penitentiar$ or correctional facilit$ or jail$ or detention centre$ or detention center$) and (guard$1 or population or inmate$ or system$ or remand or detainee$ or felon$ or offender$1 or convict$ or abscond$)).ti,ab.
12	(parole or probation).ti,ab.
13	exp *prisoner/
14	((custodial adj (care or sentence)) or (incarceration or incarcerated or imprisonment)).ti,ab.
15	(immobile or (disabled and (house bound or home bound)) or ((house or home) adj3 bound)).ti,ab. or exp *homebound patient/
16	((hous$ and (quality or damp$ or standard$ or afford$ or condition$ or dilapidat$)) or ((emergency or temporary or inadequate or poor$ or overcrowd$ or over-crowd$ or over-subscribed) and (hous$ or accommodation or shelter$ or hostel$ or dwelling$))).ti,ab. or exp *housing/
17	(rough sleep$ or runaway$1 or ((homeless$ or street or destitut$) and (population or person$1 or people or group$ or individual$1 or shelter$ or hostel$ or accommodation$1))).ti,ab. or exp *homelessness/
18	((drug$ or substance) and (illegal or misus$ or abuse or intravenous or IV or problem use$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)).ti,ab. or exp *addiction/

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19	((alcohol$ and (misus$ or abuse or problem$ use$ or problem drink$ or illicit use$ or addict$ or dependen$ or delinquency)) or alcoholic$1).ti,ab.
20	(prostitution or sex work$ or transactional sex$ or prostitute$1).ti,ab. or Prostitution/
21	(poverty or deprivation or financial hardship$).ti,ab.
22	((low-income or low income or low pay or low paid or poor or deprived or debt$ or arrear$) and (people or person$1 or population$1 or communit$ or group$ or social group$ or neighbourhood$1 or neighborhood$1 or famil$)).ti,ab. or exp *lowest income group/
23	*poverty/
24	(low$ and social class$).ti,ab.
25	(traveller$1 or gypsies or gypsy or Romany or roma).ti,ab. or exp *"Romani (people)"/
26	(mental$ and (health or ill or illness)).ti,ab. or *mental patient/ or exp *mental health/
27	(health care worker$1 or (health care adj2 service provi$) or (health-care adj2 provi$) or (((community adj1 leader$) or (community adj1 (Manag$ or advocat$ or champion$))) and (engag$ or involv$))).ti,ab.
28	(complex adj2 (patient$ or Need$)).ti,ab.
29	(outreach adj2 worker$1).ti,ab. or exp *health auxiliary/
30	(support adj2 worker$1).ti,ab.
31	(case adj2 worker$1).ti,ab.
32	(social adj2 worker$1).ti,ab.
33	social care professional$1.ti,ab.
34	((social care adj2 service provi$) or (social-care adj2 provi$)).ti,ab.
35	(((language$ or communicat$) and (barrier$ or understand$ or strateg$ or proficien$)) or translat$ or interpret$ or (cultur$ and competen$)).ti,ab. or *language ability/
36	(immigrant$ or migrant$ or asylum or refugee$ or undocumented or foreign born or (born adj overseas) or (displaced and (people or person$1))).ti,ab. Or exp *refugee/
37	exp *migrant/
38	*immigration/
39	or/2-38
40	Intervention$.ti,ab. or exp *crisis intervention/
41	((early or primary) adj2 Intervention$).ti,ab.
42	((person$ or individual or local$ or community or cultural or structural or supported or indicated or target$ or multi?component or comprehensive or pilot or media) and Intervention$).ti,ab.
43	((midstream or mid-stream) and intervention$).ti,ab.
44	(Identify$ or find or finding or locat$ or trac$ or contact$ or discover$ or detect or recruit$ or attract$).ti,ab.
45	(case finding or ((active or passive) adj3 case finding)).ti,ab.
46	((program$ or scheme$1 or service$1 or campaign$ or mobili?ation or strateg$ or measure or policy or policies) and (tuberculosis or tb)).ti,ab.
47	((case adj3 management) or case-managed).ti,ab. or *case management/ or *patient care planning/ or *case management/ or exp *health care management/
48	(case adj3 manag$ adj3 strategy).ti,ab. or continuity of *patient care/
49	((treat$ or diagnosis) and management).ti,ab.
50	((active or passive) and (Case adj3 Management)).ti,ab.
51	(risk assess$ or risk profile or risk Indicator or care plan$).ti,ab.
52	(service and (model$ or deliver$)).ti,ab. or delivery of *health care/ or *health service/
53	((primary adj3 healthcare) or ((primary adj3 health$) or care)).ti,ab. or exp *primary health care/
54	(nurse or ((general or family) adj3 (practice$ or practitioner$ or physicians$ or doctor$))).ti,ab. Or exp *nurse/ or (exp *tuberculosis/ or (tuberculosis or tb).ti,ab.)) or exp *general practice/
55	((health or extension or multi-disciplinary or multidisciplinary) and (professional$ or personal$ or practitioner or worker$ or partner$ or promot$ or provider or care team or care provider or unit or casework$ or (case adj2 work$))).ti,ab. or *health care

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	personnel/ or exp *nursing assistant/
56	(social adj2 (work$ or Support$ or Outreach)).ti,ab. or *social work/ or *social support/
57	((lay or allied or link) and (professional$ or practitioner$1 or worker$1 or advocate$1 or personnel)).ti,ab. or *paramedical personnel//
58	(volunteer$ or voluntary or charit$ or third sector).ti,ab. or *voluntary worker/ or exp *health care organization/
59	(health adj1 (center$1 or centre$1 or facilit$ or service$ or clinic$1 or hospital$1 or program$1)).ti,ab. or *public health/ or *residential care/
60	((day adj2 (care or hospital$ or patient$)) or workshop$).ti,ab. or *day care/
61	rehab$.ti,ab. or *rehabilitation center/
62	((dedicated or permanent or rapid access or fixed or TB or tuberculosis) and (clinic$1 or centre$1 or center$1 or program$)).ti,ab.
63	(((drug adj2 dependency) or substance abuse or HIV) and (unit$ or clinic$1 or centre$1 or center$1 or program$) and (tuberculosis or tb)).ti,ab.
64	(pharmac$ or dispensary).ti,ab. Or *pharmacy/
65	(communit$ or (support$ adj2 communit$)).ti,ab. or *community care/ or *health auxiliary/ or *public relations/ or *community hospital/ or *community health nursing/
66	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
67	(ambulatory adj2 care).ti,ab. or exp *ambulatory care/
68	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (health adj3 (care or work$ or practitioner$ or professional$ or service$ or center$1 or centre$1 or unit$1 or program$))).ti,ab. or *preventive health service/
69	((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (nurs$ or doctor$)).ti,ab.
70	((out adj3 hours) or (after adj3 hours) or telephone or telemedicine).ti,ab. or after-hours care/ or exp *telehealth/ or *emergency care/ or *health care delivery/
71	((walk-in or walkin or walk in) adj2 (center$1 or centre$1 or service or program$ or Clinic$1 or Session or Assesment$1)).ti,ab.
72	(drop$ adj1 in adj2 (center$1 or centre$1 or service or program$ or clinic$1 or session or meeting or assesment$1)).ti,ab.
73	(((health or home$ or house$) and (call$ or visit$)) or (home-care or home-based or (support$ adj1 hous$))).ti,ab. or Home Health Aides/ or *health auxiliary/ or exp *home care/
74	((early adj2 discharge) or (recent$ adj2 discharged) or (out adj2 patient)).ti,ab. or *patient care/ or *outpatient department/
75	(counselling or counseling or counsellor or counselor or (integrated counselling adj1 testing centre$1) or (integrated counselling adj1 testing center$1) or ICTC).ti,ab. or *counseling/ or *directive counseling/
76	((help adj2 group$) or (self adj2 help) or support$ or (peer adj2 peer)).ti,ab. Or *self help/
77	(collaborat$ or shared or (integrated adj1 care$) or ICP or network$ or co-locat$ or (one adj1 stop)).ti,ab. or *integrated health care system/
78	((health adj2 education) or (skill adj2 mix) or (role adj2 develop$) or leadership or ((interdisciplinary or inter-team or Professional or team) adj2 communicate$)).ti,ab. or exp *health education/ or exp *interdisciplinary communication/ or *leadership/ or *doctor patient relation/ or *nurse patient relationship/ or patient relationship*.ti,ab.
79	((outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium) and (tuberculosis or tb)).ti,ab.
80	or/40-79
81	test$.ti,ab.
82	(examination$1 or assessment$1 or identification or assay$ or detection).ti,ab.
83	diagnosi$.ti,ab. or *diagnostic test/

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84	((chest adj2 x?ray) or chest radiograph or MXU).ti,ab. or *thorax radiography/
85	(screen$ or (new$ adj1 screen$)).ti,ab.
86	(monitor$ or sampling).ti,ab.
87	((target$ or focus$ or community or population or individual$ or person$ or opportunistic or coerc$ or voluntary or initiated) and (test$ or diagnosis or screen$ or assay$ or detection)).ti,ab.
88	PIT.ti,ab.
89	provider initiated test$.ti,ab.
90	((rapid or prompt or quick$ or earl$ or (point adj2 care)) and (test$ or screen$ or diagnosi$ or assay$ or detection)).ti,ab.
91	((provider or anonymous or accurate or support$ or incentiv$ or counsel$) and (test$ or diagnosis or screen$ or assay$)).ti,ab. or *anonymous testing/
92	(test$ adj2 (center$1 or centre$1 or unit$1 or setting)).ti,ab.
93	or/81-92
94	(acceptability or acceptable or attend$ or access$ or availab$ or non-attend$ or increas$ or promot$ or opt$ or particip$ or adhere$ or involvement or uptake or take-up or utiliz$ or utilis$ or refus$ or referr$ or self-referr$ or self-report$ or barrier$ or decreas$ or isolation or interven$ or aware$ or opportunit$ or advice or information or incentiv$ or recruit$ or find or finding or compliance or comply or retain or retention or provision or encour$ or usage).ti,ab.
95	(socio sanitary support or reimburs$ or (social adj2 support) or ((cash or financial or money or monetary or economic or voucher or credit or drug$1 or methadone or telephone) adj2 (benefit$ or support or incentive or assist$ or credit))).ti,ab.
96	(((lifestyle or behavio?r) adj2 (therapy or modif$ or chang$ or adapt$ or adopt$)) and (tuberculosis or tb)).ti,ab. or *social marketing/
97	*marketing/
98	*attitude to health/
99	*health care delivery/
100	*access to information/
101	*confidentiality/
102	*Health education/
103	*health promotion/
104	*patient attitude/ or *refusal to participate/ or *treatment refusal//
105	*patient compliance/
106	*motivation/
107	Stigma.ti,ab.
108	*prevalence/
109	*patient participation/
110	or/94-109
111	treat$.ti,ab. or Treatment Outcome/
112	(directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. Or *directly observed therapy/
113	(disease management or (treat$ and (management or control))).ti,ab.
114	((adherence or compli$ or non-compli$ or default$ or finish$ or Retention or attrition or (drop adj1 out) or disappear$ or abscond$) and treat$).ti,ab. or exp *patient compliance/
115	((referr$ or self-referr$ or (self adj diagnos$)) and treat$).ti,ab.
116	((suitab$ or eligib$) and treat$).ti,ab.
117	((follow adj1 up) or discharge).ti,ab. or *follow up/
118	((positive or negative) and test).ti,ab.
119	((interrupt$ or relapse$ or stop$ or cessation or with?ld$ or avoidance or (lost adj2 follow)) and treat$).ti,ab. or *treatment withdrawal/
120	((medicine$1 or drug or treat$) and (regimen or adherence)).ti,ab. or exp *self care/
121	(treat$ and (appointment$ or Schedule$)).ti,ab. or *patient scheduling/
122	((care adj2 seeking) and pathway$).ti,ab.
123	((case adj3 management) or case-managed).ti,ab. or Case Management/ or *patient care planning/ or *health insurance/
124	(case adj3 manag$ adj3 strategy).ti,ab. or continuity or *patient care/

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125	((case or treat$ or diagnosis) and management).ti,ab.
126	((active or passive) and (case adj3 management)).ti,ab.
127	((risk assessment or care plan$) and (case adj3 management)).ti,ab.
128	or/111-127
129	1 and 39 and (80 or (93 and (110 or 128)))
130	limit 129 to yr="1990 -Current"
131	limit 130 to "english language"
132	(animal$ or badger$ or Cow$ or Cattle or bovine).ti,ab. or (animals/ not humans/)
133	131 not 132
134	limit 133 to yr="1990 - 2010"
135	130 not 132
136	135 not 134
137	(albania or bulgaria or cyprus or croatia or latvia or lithuania or luxembourg or malta or montenegro or romania or serbia or yugoslav or turkey).ti,ab,hw,in.
138	1 and 135 and (80 or (93 and (110 or 128)))
139	limit 138 to yr="1990 -Current"
140	139 not 132
141	140 not 135
142	136 or 141

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Supplementary Material IV: Evidence Statements

Grading of evidence

No evidence – no evidence or clear conclusions from any of the studies;
Weak evidence – no clear or strong evidence/conclusions from high quality studies and only tentative evidence/conclusions from moderate quality studies or clear evidence/conclusions from low quality studies;
Moderate evidence – tentative evidence/conclusions from multiple high quality studies, or clear evidence/conclusions from one high quality study or multiple medium quality studies, with minimal inconsistencies across all studies;
Strong evidence – clear conclusions from multiple high quality studies.

Tuberculosis identification

Evidence statement 1: Effectiveness of using different types of healthcare workers on improving identification of active TB
1·1 **Conflicting evidence** arose concerning types of healthcare workers to improve TB screening. Aldridge et al., 2015 [+] showed that the uptake of TB screening did not improve when peers encourage and educate homeless people, compared to shelter personnel.[1] On the contrary, Duarte et al. 2011 [-][2] and Goetsch et al. 2012 [-][3] showed an increase in uptake of TB screening amongst homeless people and drug users after involving community health workers (CHW) and key partners in the education and promotion of TB screening. The results demonstrated by Goetsch et al. fluctuated over the study period and both studies retrospectively compared the findings over different time periods, which might be an important source of bias. 1·2 **Moderate evidence** from two studies focussing on the identification of TB contacts by using peers. One study identified by this review, Ospina et al. 2012 [+], showed that contact tracing among migrants improved significantly by using CHWs from the same migrant community to coordinate contact tracing.[4] The comparison group was recruited over a different time period, which reduced the quality of this study. Ricks, 2008 [++],[5] identified by the NICE review,[6] suggested that contact tracing of drug users with active TB improved by using former drug users compared to healthcare workers. It was unclear if the improvement could be contributed to the use of peers, as the study also used enhanced case management for the peer-led intervention group, the control group received limited case management.

Evidence statement 2: Effectiveness of using different settings on improving identification of active TB
2·1 **Weak evidence** from Jit et al. 2011 [+] showed that a mobile TB service is an effective intervention to identify hard-to-reach individuals with TB as 35% of the cases identified by this mobile

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TB service were asymptomatic.[7]

Four studies were identified by the NICE review,[6] providing the following evidence:

2·2 **Weak evidence** from Mor et al., 2008 [-] suggesting that pre-migration screening in Ethiopian migrants reduced the risk of developing active TB in Israel and reduced the time from entry into the host country (Israel) until TB diagnosis compared to post-migration screening.[8] The study compared two migrant groups recruited over two different time period what limited the quality of the findings.

2·3 **Weak evidence** from El-Hamad et al., 2001 [+] suggesting that active case finding conducted in a TB clinic improved TB screening completion among migrants compared to TB screening conducted in a non-specialist primary care facility.[9] However, the study did not adjust for the differences in baseline characteristics.

2·4 **Weak evidence** from Bothamley et al., 2002 [-] showing that TB screening by symptom-based questionnaire was less useful in port-of-arrival clinics compared to homeless centres.[10] In 90.9% of the migrants screened by questionnaire further TB screening was conducted compared to 100% of the questionnaire screened homeless people. The study findings were limited as the study compared two different hard-to-reach groups in two different settings.

2·5 **Weak evidence** from Miller et al., 2006 [+] suggesting that there was no significant statistical difference in screening uptake in the homeless centre where screening was optional and a prison where screening was mandatory, however, the homeless people received incentives for TB screening.[11] In the homeless centre more cases were detected but different methods were used. The evidence was weak as the study compared two groups with possibly different baseline characteristics, different TB prevalence and different tests were offered.

Evidence statement 3: Cost-effectiveness of using different settings on improving identification of active TB

3·1 **Weak evidence** from Jit et al. 2011 [+] that a mobile TB service is cost-effective, the incremental cost ratio for the screening service was £18,000 per Quality of Life Year (QALY) gained.[7]

A further two studies were identified by the NICE review:[6]

3·2 **Weak evidence** from Mor et al., 2008 [-] suggesting that pre-migration screening in Ethiopian migrants would save Israel $449,817 over a five year period.[8] Different sources were used for the cost analysis, with varying reliability, limiting the findings.

3·3 **Weak evidence** from Bothamley et al., 2002 [-] showed that TB screening among migrants as part

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of the port-of-arrival programme had a cost-saving of £12.70 per person screened, it would costs an additional £0.50 per person screened at a homeless centre and £7.00 per migrant screened at a general practice.[10] The findings of this study are limited as the study compared two different populations with possible different characteristics and TB prevalence.

Tuberculosis management

Evidence statement 4: Effectiveness of using different types of healthcare workers on improving management of active TB
Moderate evidence from one study identified by the NICE review[6], Ricks, 2008 [++], suggested that drug users receiving enhanced case management by peers were more likely to complete TB treatment than drug users who received limited case management by healthcare workers (RR = 2.68, 95%CI 1.24-5.82; p = 0.01).[5] The findings of this study are limited as the intervention group received enhanced case management and were managed by peers, therefore it is unclear which of the two contributed (more) to the improved treatment outcome.

Evidence statement 5: Effectiveness of using different settings on improving management of active TB
5·1 **Weak evidence** from Jit et al. 2011 [+] that treatment completion rate in patients treated by the mobile 'Find and Treat' service was higher (67.1%) than in the patients receiving standard care at a TB clinic (56.8%) and lost to follow-up rate in the patients treated by the mobile 'Find and Treat' service was lower (2.1%) than in the patients receiving standard care at a TB clinic (17.2%).[7] 5·2 **Weak evidence** from Deruaz & Zellweger, 2004 [-], showed that there was no statistical difference in treatment outcome when directly observed treatment was delivered at the healthcare facility or at a convenient site in the community in mixed hard-to-reach groups.[12] The findings were limited by a potential selection bias and the way the treatment outcome was collected differed in both groups.

Evidence statement 6: Cost-effectiveness of using different settings on improving management of active TB
6·1 **Weak evidence** from Jit et al. 2011 [+] that a mobile TB management service is cost-effective, the incremental cost ratio for the service was £4,100 per Quality of Life Year (QALY) gained.[7]

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Supplementary Material V: Data extraction forms

Study details	Population and setting	Method of allocation to intervention/ control	Outcomes and methods of analysis	Results	Note by review team
Year: 2015 **Country:** United Kingdom (UK) **Authors:** Aldridge R.W., Hayward A.C., Hemming S. et al.[1] **Citation:** Aldridge R.W., Hayward A.C., Hemming S. et al. Effectiveness of peer educators on the uptake of mobile X-ray tuberculosis screening at homeless hostels: a cluster randomised controlled trial. *BMJ open* 2015; **5**: e008050. **Aim of study:**	**Source population(s):** Homeless people **Eligible population:** Hostels for homeless people in London, UK **Selected population:** Homeless people at hostels in London, UK All hostels in London who participated in 2 previous screening sessions were eligible for inclusion. Eligible hostels had not been screened in the 6 months prior to the scheduled mobile X-ray Unit (MXU) screening session. **Excluded population:**	**Method of allocation:** Sites were randomized to intervention or control group by Sealed EnvelopeTM http://www.sealedenvelope.com/) which ensured allocation concealment until interventions were assigned. To ensure comparability between intervention and control arms, hostels were stratified on the basis of their size (binary variable indicating whether hostels had more than 43 beds) and previous screening uptake level (binary variable indicating whether hostels had greater than 50% historical	**Primary outcomes:** The number of eligible clients at a hostel venue screened for active pulmonary tuberculosis by MXU **Secondary outcomes:** Secondary analysis was also conducted by subgroups, for large and small hostels separately, and low and high previous screening uptake level using the binary categorical variables described previously for these analyses. **Method of analysis:** The study statistician conducted analysis blinded to the allocation of	**Primary results:** Control sites: - 1,192 residents - Median uptake of 45% (inter-quartile range (IQR):33,55) Intervention sites: -1,150 eligible residents - Median uptake of 40% (IQR:25,61) Poisson regression to account for the clustered study design, hostel size and historical screening levels, there was no evidence that peer educators increased uptake (adjusted risk ratio 0.98; 95% confidence interval (95%CI): 0.80,1.20). **Secondary results:** No evidence was found for peer educators	**Limitations identified by author:** - The study design was not powered to detect a difference in tuberculosis cases identified by the two arms as this would require considerably larger sample sizes and would have meant repeated screening at hostels, potentially diluting the effect of the intervention during the study - Unable to collect individual data as part of the study as this would have required individual consent and would have been challenging logistically given that screening took place within an operational setting where any data collection would have

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To compare current practice for encouraging homeless people to be screened for tuberculosis by a mobile digital X-ray unit in London, UK, with the additional use of volunteer peer educators who have direct experience of tuberculosis and homelessness. **Study design:** Cluster randomised controlled trial **Quality score:** + **Applicability:** ++	- Hostels with uptake levels over 80% were excluded from the study – as low chance of intervention having impact - Not allowing peers on the venue **Setting:** Homeless hostels in London, UK **Sample characteristics:** Majority of hostels had 43 or less beds, reported a historical screening uptake of >50% and provided no incentives for screening.	uptake). A cluster randomised design was chosen as the intervention was aimed at the hostel sites rather than individuals clients **Intervention(s) description:** Peers moved around the hostel in conjunction with hostel staff and spoke to residents in order to encourage them to attend screening. **Comparator/ control(s) description:** Encouragement by hostel staff **Baseline comparisons:** Proportion of people screened for TB **Study sufficiently powered?:** Yes, power calculation done before hand, met the sample size	intervention or control arms. Poisson regression analysis was used to analyse outcome events at screening hostels. Bed occupancy level was included as the exposure variable, screening uptake as the outcome (or indicator) variable, and hostel venue as a random effect to account for clustering at each site. The analysis was adjusted by inclusion of the randomisation stratification factors of historical uptake rates and bed size. **Modelling method and assumptions:** Clustered analysis, assuming that characteristics of the populations at respective hostels were comparable. **Time horizon:** February 2012 and	increasing uptake of screening for any of the other secondary analyses. The study team noted no adverse events.	interrupted the flow of screening and caused unacceptable delays for service users - Peers may lack technical knowledge and the confidence with which to challenge some of the client misconceptions and concerns that reduce screening uptake - Most effective when complemented i.e. delivered in conjunction with professionals **Limitations identified by review team:** - Hostels with high uptake were excluded = bias risk - Most sites were not naïve to peer intervention **Evidence gaps and/or recommendations for future research:** - Any difference in uptake with previous screening sessions? - Effectiveness of using

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		requirement of 1045 individuals, or approximately 21 hostels in each arm	October 2013		peers as a standalone intervention versus peers working alongside professionals and this remains an important research question. **Source of funding:** NIHR and Welcome Trust. **Conflict of interests:** None for most authors - AS (last author) is clinical lead for the Find and Treat service including the mobile digital X-ray unit.

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Year: 2012 **Country:** Germany (Frankfurt/Main) **Authors:** Goetsch U., Bellinger O.K., Buettel K.L., Gottschalk R.[2]	**Source population(s):** Homeless & drug users **Eligible population:** Homeless & drug users recruited from homeless and drug services in Frankfurt/Main	**Method of allocation:** Not applicable (NA) **Intervention(s) description:** Community health worker educated staff and users of services for homeless and drug users about TB	**Primary outcomes:** Feasibility and sustainability of a TB programme focussing on TB education and voluntary X-ray investigation in homeless and drug users **Secondary**	**Primary results:** It is feasible when included in already existing public health services **Secondary results:** - No. CXR: 10/month in homeless & 9/month in drug users After intervention	**Limitations identified by author:** - Selection bias, illegal immigrants might avoid authorities - Small number of TB patients makes it difficult to say anything about age and gender differences - No data on length of

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Citation: Goetsch U., Bellinger O.K., Buettel K.L., Gottschalk R. Tuberculosis among drug users and homeless persons: impact of voluntary X-ray investigation on active case finding. *Infection* 2012; **40**: 389-95. **Aim of study:** To evaluate the feasibility and sustainability of the program, its coverage and both the case-finding rates and characteristics of cases. Also to assess the treatment outcomes **Study design:** Before and after comparison **Quality score:** - **Applicability:** +	**Selected population:** All subjects seen at the Public Health Department for chest X-rays (CXR) and fulfilling the criteria for homeless (stayed at shelter for >2 nights) /drug users (attend day-care facilities, night shelter for drug users or needle exchange programme) **Excluded population:** Patients with tuberculosis (TB) symptoms detected in clinics and notified through the Protection against Infection Act **Setting:** Community health worker (CHW) went to services to promote CXR – CXR performed at Public Health Department **Sample**	transmission and promoted voluntary CXR at Public Health Department 1x/year or at least 1x/2years Community Health Worker obtained the medical history through standardised questionnaire CXR read by TB physician – referral and follow up test in a clinic could be initiated immediately Suspicion for active TB – CHW took care of further diagnostics and follow up Active TB needed hospitalisation for treatment CHW kept contact with doctors/social workers 2x/month, later monthly Contact tracing in shelter HIV was only notified in active TB	**outcomes:** Estimate the coverage of the programme, assess other risk factors and determine TB rates & treatment outcome in the 2 groups **Method of analysis:** - t-test or analysis of variance for continuous variables - chi-square test or Fisher's exact test for categorical data **Modelling method and assumptions:** - Multivariate logistic regression effect of risk groups, birth place, age & gender **Time horizon:** 1 May 2002 – 30 April 2007	46/month in homeless & 25/month in drug users <u>Coverage:</u> - Screening 1x/2 years: 18% of drug users & 26% of homeless - Screening every year: 10% of drug users & 15% of homeless (based on the range of drug users & homeless people between 6,416 and 9,000 individuals in Frankfurt/Main) - Chao's heterogeneity model: 18-26.3% 1 CXR/2 years - 2002-2004: 18.0% - 2003-2005: 19.3% - 2004-2006: 26.4% - 2005-2007: 23.4% and 10-15% CXR/year - 2002-2004: 10.0% - 2003-2005: 10.7% - 2004-2006: 15.0% - 2005-2007: 23.4% <u>Case finding:</u> - 39 TB cases in 5 years: 14 drug users & 25 homeless = 8.7% of total TB cases in Frankfurt - 19 cases smear +, 7	drug use and homelessness - The impact of HIV can't be estimated - Unknown fluctuations of the study population make the denominator unstable **Limitations identified by review team:** - Patients had to travel to the public health department - Comparison over time, important confounder - Not adjusted for distance from service to public health department **Evidence gaps and/or recommendations for future research:** Use a control group and use of mobile CXR unit to increase screening uptake **Source of funding:** Not recorded (NR) **Conflict of interests:** None

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	characteristics: 4,529 CXRs in 3,477 people - 66% homeless - 34% drug users <u>Homeless:</u> - 40.9 years ± 12.5 years - 90.1% male - 29.6% foreign born <u>Drug users:</u> - 35.8 years ± 8.3 years - 76.2% male - 28.0% foreign born (increased over study period → 2002: 15%, 2007:37%)	patients **Comparator/ control(s) description:** Before intervention – no CHW who gave TB education and promoted CXR **Baseline comparisons:** Coverage of CXR screening before and after intervention **Study sufficiently powered?:** Low number of active TB cases		smear –ve but culture +ve - 13 cases clinical/ radiological diagnosis - Case finding rate 861/100 000 CXRs - Drug users 10/14 HIV +ve, homeless 1/25 HIV +ve ($p<0.001$) No significant difference in case-finding rates according to gender (906/100,000 for men vs. 601/100,000 for women; $p = 0.43$), place of origin (906/100,000 for natives vs. 752/100,000 for foreign born; $p = 0.61$) or between the risk groups (888/100,000 for the homeless vs. illegal drug users (816/ 100,000; $p = 0.80$). Logistic regression model with the risk factors age, gender, risk group and place of origin: age was the only variable to be associated with the risk of TB and the variable risk group was an effect modifier	

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				Treatment completion - 76.3% (29/38) completed treatment (one patient left Frankfurt to unknown destination before completion of treatment, excluded from analysis of treatment completion) – of which 19 homeless people and 10 drug users - 5 people needed admission because of non-compliance (3 drug users, 2 homeless) - 5 people died of other causes than TB (3 homeless and 2 drug users) - 4 people stopped treatment (lack of compliance) – 10.5% No difference in the treatment outcome between the two risk groups (p = 0.96), and age, gender or HIV-status did not have any significant effect on treatment outcome.	

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Study details	Population and setting	Method of allocation to intervention/ control	Outcomes and methods of analysis	Results	Note by review team
Year: 2012 **Country:** Spain, Barcelona **Authors:** Ospina J.E., Orcau A., Millet J-P. et al.[3] **Citation:** Ospina J.E., Orcau A., Millet J-P. et al. Community health workers improve contact tracing among immigrants with tuberculosis in Barcelona. *BMC public health* 2012; **12**: 158. **Aim of study:** To evaluate the effectiveness of an intervention with CHW to improve contact tracing among immigrants **Study design:**	**Source population(s):** Migrants **Eligible population:** Migrants in Barcelona **Selected population:** All TB cases registered by the TBPCP (the Barcelona TB Control Program) between January 1st 2000 and December 31st 2005, and resident in the city of Barcelona were included **Excluded population:** Not registered TB patients **Setting:** Barcelona TB program **Sample**	**Method of allocation:** All TB cases registered at TBPCP **Intervention(s) description:** Community health workers (CHW) actively follow up the cases and contacts, visit the cases at home, accompany case to outpatient appointments, provide counselling and information on treatments. Educational sessions in health care centres, private homes and immigrant associations. Assistance with obtaining residence permits, housing, food banks, public dining halls and health card application.	**Primary outcomes:** The influence on contact tracing of CHW intervention **Secondary outcomes:** The influence on contact tracing of other variables: sex, age, hospital of diagnosis, district of residence, birthplace, HIV, homeless **Method of analysis:** - Descriptive analysis was performed by calculating proportions - The median and interquartile range were calculated for quantitative variables - Categorical variables were compared using the X^2 test. Odds ratio (OR) and 95%CI were calculated as a measure of	**Primary results:** - The increase in contact tracing coverage of contacts of smear positive PTB and all clinical forms of TB in the intervention period was statistically significant * 81% (post) vs 65.7% (pre) *OR = 1.6 (95%CI = 1.2-2.0) * Adjusted OR 1.8 (95%CI: 1.3-2.5) $p < 0.001$ - CHW intervention had an aOR of 2.4 (95%CI: 1.3-4.3) p=0.005 to fail contact tracing for smear-positive cases and an aOR of 1.8 (95%CI: 1.3-2.5); p = 0.001 for all TB cases **Secondary results:** - Factors associated with failure to conduct contact tracing for	**Limitations identified by author:** - Variation in characteristics between both periods; an increase of cases between 25-39 years of age, from Latin America and India, Pakistan and from inner-city in the CHW group. The increase in immigrants would most likely have worsened contact tracing and therefore our figures may have underestimated the benefit of the CHW intervention. **Limitations identified by review team:** - Wide 95% CI's smear +ve making the OR less precise for: * Hospital D * Area of origin * District of residence unknown *HIV +ve

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Quasi-experimental study with historical pre-post comparison **Quality score:** + **Applicability:** ++	**characteristics:** 572 cases pre-intervention & 388 post-intervention **Pre-intervention** - 202 (35.3%) were from Latin American countries -136 (23.8%) from India or Pakistan - 92 (16.1%) from North Africa - 142 cases (24.8%) from other countries - Majority men - 25-39 years - 72.2% Pulmonary TB - 35.3% smear +ve - 34.4% lived in inner city **Post intervention** - 152 (39.2%) were from Latin American countries - 112 (28.9%) from India or Pakistan - 42 (10.8%) from North Africa - 16 (4.1%) from Sub-Saharan Africa - 66 cases (17%) from other countries	**Comparator/ control(s) description:** Pre-intervention **Baseline comparisons:** Pre- /post-intervention contact tracing was compared **Study sufficiently powered?** Yes; 95% CI sufficiently narrow	association. **Modelling method and assumptions:** Stepwise backward logistic regression; variables lacking significant association measures in univariate analysis were assumed not to be confounders. **Time horizon:** 1st 2000 and December 31st 2005	smear +ve TB include: * Diagnosed in hospitals B and D * Birthplace in India-Pakistan or North Africa * Unknown district of residence * HIV infection * Homeless - Factors associated with failure to conduct contact tracing for all forms of TB include: * Male * Hospitals B and D * Birthplace other than Latin American countries * Unknown district of residence * Incarceration history * Homeless * Index who had culture-negative or extra-pulmonary TB or had a normal chest X-ray - Of all TB cases identified among foreign born people, 79.4% were seen by CHWs, 12.4% were contacted directly by	* Homeless - Wide 95% CI's all TB: making the OR less precise for: * District of residence unknown * Incarceration * Homeless 95% CI's crossing 1 in hospital D **Evidence gaps and/or recommendations for future research:** - Studies on cost-effectiveness of the CHW interventions in the TB programs **Source of funding:** NR **Conflict of interests:** None

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	- Majority men - 25-39 years - 73.2% Pulmonary TB - 39.2% smear +ve - Almost 50% lived in inner city			the public health nurse and the remaining 8.2% could not be contacted - Active follow up in 194 TB cases and contact census, a total of 293 counselling sessions, 147 linguistic mediation session, 264 individualised and 97 group educational sessions about TB, 280 home visits, 70 hospital visits and 5,935 telephone calls (a median of 15.3 calls per case) were performed	

Study details	**Population and setting**	**Method of allocation to intervention/ control**	**Outcomes and methods of analysis**	**Results**	**Note by review team**
Year: 2011 **Country:** Portugal **Authors:** Duarte R., Santos A., Mota M. et al.[4]	**Source population(s):** Drug users in Vila Nova de Gaia, Portugal **Eligible population:** Drug users in Vila Nova de Gaia	**Method of allocation:** Before and after 2004 – intervention was implemented in 2004 **Intervention(s) description:** After 2004:	**Primary outcomes:** Diagnosis of active TB, treatment compliance before and after intervention **Secondary outcomes:** OR and 95%CI to measure association	**Primary results:** 2001-2003: - 125 drug users observed in CDP of which: * 52 drug users were screened for TB (100% male, mean age 32 years) * 73 drug users were	**Limitations identified by author:** - Not a controlled trial - Risk for bias - Unknown what part of the intervention contributed to the outcome

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Citation: Duarte R., Santos A., Mota M. et al. Involving community partners in the management of tuberculosis among drug users. *Public Health* 2011; **125**: 60-2. **Aim of study:** To evaluate the effect of the intervention on diagnosis of TB and treatment compliance **Study design:** Retrospective review of records Comparison before and after intervention (2004) **Quality score:** - **Applicability:** +	(VNdG), Portugal Population VNdG: 290,000 Estimated number of drug users = 4.3-6.4 per 1,000 inhabitants **Selected population:** Screening and treatment records for all drug users visiting Chest Disease Centre (CDP) between 2001-2007 **Excluded population:** NR **Setting:** All drug users screened and treated at the outpatient TB clinic (Chest Disease Centre) 2001-2007 were reviewed **Sample characteristics:** 2001-2003: - 125 drug users @CDP - 52 screened (100%	Intervention to improve early identification and treatment of drug users with TB. The key partners (outpatient TB clinic, drug users support centres, shelters and street teams, local public health department and the local hospital) identified drug users in their population - Promotion of health-seeking behaviour - Notification card for screening in CDP - Elimination of potential barriers: * Street teams offered free transport *All care at CDP free of charge - Encouraged referral but tried to manage TB screening locally - Seriously ill: immediate referral to CDP/local hospital (with transport and attendance)	**Method of analysis:** OR and 95%CI were used to measure the strength of the association **Modelling method and assumptions:** Improve early identification and treatment of drug users with TB **Time horizon:** 2001-2003 Intervention 2005-2007	referred to CDP because of symptoms or following discharge from hospital with diagnosis TB Of all drug users observed at CDP; 82 drug users (65.6%) were diagnosed with active TB of which 11 drug users (13.4%) were identified by screening Treatment compliance: - 47.6% poor compliance - 35.4% stopped TB treatment TB in VNdG 2001-2003: - 515 TB cases of which 82 were drug users - 32 TB cases died of which 15 were drug users (OR 4.66, 95%CI 2.24 - 9.70). - TB/HIV co-infection: 63 (71%) 2005-2007: (after implementation of the programme) - 465 drug users were screened for TB (86%	**Limitations identified by review team:** - Retrospective design = risk of bias - Methods not well described - Unknown what percentage did not come for screening (how many people recruited for screening) - Difference in time zone = risk for confounders, might have been on the political agenda, been on the news etc. = bias - Low precision of estimates of effects (indicated by wide 95%CI) probably due to small sample size **Evidence gaps and/or recommendations for future research:** - Case-control trial to compare 2 different cities (one with intervention other without intervention - Check cost-effectiveness **Source of funding:**

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	male, mean age 32 years) - 73 for symptoms or following discharge with diagnosis TB 2005-2007: - 465 screened (86% male, mean age 36 years) - 30 for symptoms or following discharge with diagnosis TB **Study definitions:** Active TB: culture *M. tuberculosis* or clinical & radiology criteria Latent TB: asymptomatic individuals with normal chest radiography and positive TST (TST > 5 mm in immune-compromised persons, TST > 10 mm in immune-competent persons)	At CDP: - Screening: symptom questionnaire, tuberculin skin test (TST) & CXR: annual screening/after contact/symptoms - Directly observed therapy short-course (DOTS) at CDP, combined with other medical treatment/ drug abuse treatment - CDP offered HIV testing in case of active TB **Comparator/ control(s) description:** Before 2004: - Drug users referred to CDP with a diagnosis of TB after diagnosis from hospital – Treatment was not compulsory – To improve compliance: info was provided, psychosocial support, full treatment to patient and family (if		male, mean age 36 years) - 30 drug users were referred to CDP because of symptoms or following discharge from hospital with diagnosis TB Of all drug users seen at the CDP, 59 drug users (11.9%) were diagnosed with active TB of which 36 drug users (61%) were identified by screening Treatment compliance: - 23.7% poor compliance - 10.2% stopped treatment TB in VNdG 2005-2007: - 386 TB cases of which 59 were drug users - 19 TB cases died of which 8 were drug users (OR 4.66, 95%CI 1.79 - 12.15) - TB/HIV co-infection: 37 (64%) Conclusion: The number of screened	None **Conflict of interests:** None **Ethical approval**: Yes, approved by the CDP de Vila Nova de Gaia body

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		needed), transport & free breakfast. - No active screening policy **Baseline comparisons:** Number of TB cases screened **Study sufficiently powered:** NR but wide 95%CI		drug users had increased, therapy was available to a higher proportion of TB cases and active TB treatment compliance had improved significantly **Secondary results:** - Drug users screened for TB without symptoms: OR 21.8; 95%CI 13.0-36.3 - Drug users with active TB: OR 10.1; 95%CI 4.44-23.0 - Poor compliance: OR 0.34; 95%CI 0.16-0.72 - Treatment stopped OR 0.21; 95%CI 0.08-0.54 - % of drug users under TB cases OR 0.95; 95%CI 0.66-1.37 - Mortality due to TB decreased from 18.3% in 2001- 2003 to 13.6% in 2005-2007 among drug users (OR 0.7, 95%CI 0.28 - 1.78). - TB/HIV co-infection decreased from 63 (71%) in 2001-2003 to	

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				37 (64%) in 2005-2007 (OR 1.37, 95%CI 0.68-2.78).	

Study details	Population and setting	Intervention/comparator	Outcomes and methods of analysis	Results	Note by review team
Year: 2011 **Country:** UK **Authors:** Jit M. Stagg H.R., Aldridge R. et al.[5] **Citation:** Jit M. Stagg H.R., Aldridge R. et al. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. *BMJ* 2011; **343**: d5376. **Aim of study:** To assess the cost effectiveness of the Find and Treat	**Source population(s):** Hard-to-reach individuals **Eligible population:** Hard-to-reach individuals with active pulmonary tuberculosis **Selected population:** Hard to reach individuals with active pulmonary tuberculosis screened or managed by the Find and Treat service **Excluded population:** - Cases with extra-pulmonary tuberculosis - Latent tuberculosis - Suspected	**Method of allocation:** NA **Intervention(s) description:** All individuals are screened on voluntary basis. 1. Mobile X-ray screening clinic visited locations where high-risk groups could be found (homeless shelters, drug treatment centres, criminal services, street outreach etc.) 2. Raise awareness 3. Under take case holding 4. Provide support for treatment completion (supported by peer workers)	**Primary outcomes:** Incremental costs, quality adjusted life year (QALY), for the Find and Treat service. **Secondary outcomes:** Cost-effectiveness ratios for the Find and Treat service **Method of analysis:** NR **Modelling method and assumptions:** - Discrete, multiple age cohort, compartmental model to model a population of individuals with active tuberculosis 4 groups:	**Primary results:** The model estimated that, on average, the Find and Treat service identifies 16 and manages 123 active cases of tuberculosis each year in hard to reach groups in London. The service has a net cost of £1.4 million/year and, under conservative assumptions, gains 220 QALYs. The incremental cost effectiveness ratio was £6,400-£10,000/QALY gained (about €7300-€11,000 or $10,000-$16,000 in September 2011). - 22.9% of patients detected by the mobile screening unit with the longest delays between symptom onset and	**Limitations identified by author:** - Absence of randomisation of tuberculosis cases to be either managed or not managed by the Find and Treat service - The service also manages extremely hard to reach individuals, who are often already lost to follow-up at the time of referral or who would never present for care without the mobile screening unit. Hence the comparison of cases with retrospective controls probably underestimates the incremental benefit of the service, although we cannot be certain without a randomised

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service for diagnosing and managing hard to reach individuals with active tuberculosis in London **Study design:** Economic evaluation using a discrete, multiple age cohort, compartmental model of treated and untreated cases of active tuberculosis. **Type of economic analysis:** Cost-effectiveness **Economic perspective:** Healthcare taxpayer perspective **Internal validity:** Yes **Quality score:** ++ **Applicability:** +	tuberculosis - Cases merely receiving prophylaxis (and hence unlikely to have active tuberculosis) - Cases for which the diagnostic delay could not be calculated - Cases younger than 16 years **Setting:** London, United Kingdom. **Sample characteristics:** - 48 mobile screening unit cases - 188 cases referred for case management support - 180 cases referred for loss to follow-up - 252 control cases, TB cases that presented to a TB clinic themselves, without intervention of the Find and Treat service (current method of passive case finding)	**Comparator/ control(s) description:** Controls: passively detected cases with active pulmonary tuberculosis (individuals who presented to London tuberculosis services on their own accord without screening and referral to the Find and Treat service - notified to the Health Protection Agency's enhanced tuberculosis surveillance system between 1 January 2009 (when the system began recording risk factor information) and 9 August 2010. Controls were age matched with actively detected cases (within five year age categories) and had to display one or more risk factors (a history of homelessness or imprisonment, drug	- Active untreated tuberculosis - Active treated tuberculosis with up to 125 days of continuous treatment - Active treated tuberculosis with more than 125 days of continuous treatment - Lost to follow-up 4 final outcomes: - Completion of treatment - Death due to tuberculosis related causes - Death due to other causes - Other final outcomes that the Find and Treat service is not expected to change (such as patients being transferred out of London or stopping treatment for clinical reasons). <u>Assumptions:</u> - The cost of a new mobile unit £600,000 were added to the	treatment presentation were unlikely to present for treatment without the activities of the Find and Treat service - 35.4% of mobile screening unit patients were asymptomatic on detection, and hence would not have presented for treatment without the unit. - Once on treatment, mobile screening unit cases managed by the Find and Treat service had a much lower risk of loss to follow-up than passively presenting controls (loss to follow-up probability after one year: 2.1% for cases, 17.2% for controls) - Cases referred to Find and Treat because of complex case management issues had higher rates of completing treatment (61.2% after one year) and lower rates of loss to follow-up (3.3% after one year) than controls **Secondary results:** - Every year the service	study - Did not incorporate secondary transmission into the economic evaluation, even though the mobile screening unit in particular probably averts several secondary cases by finding highly infectious individuals. - Did not measure the effect of the Find and Treat service on reducing the likelihood of patients developing and transmitting acquired drug resistance (as a result of poor treatment adherence). Drug resistance increases the duration and costs of treatment, as well as the risk of severe disease, thus prevention could be an important benefit of the service. **Limitations identified by review team:** Small group of PTB in intervention group

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	Economic analysis data source: Find and Treat database for information (including risk factors and clinical information) of individuals, diagnosed with PTB (between Sep 2007-Sep 2010) The control group (TB cases that presented on their own accord to a TB clinic) was obtained from the Health Protection Agency between Jan 2009 and Aug 2010. Risk factors and clinical information for the controls were obtained from the enhanced tuberculosis surveillance system.	or alcohol abuse, or mental health problems). **Baseline comparisons:** Compared: - Having no Find and Treat service, - Having only one part of the service (the mobile screening unit or the case management component) - Having both parts of the service **Study sufficiently powered:** NR but a small number of PTB cases in the Find and Treat group	costs of the first year of the service, with discounted costs and outcomes totalled over five years - Costs of £8,300 and £75,000 for treatment of DS-TB and MDR-TB - Only 50% of asymptomatic cases with a positive result from the mobile screening unit would progress to symptomatic disease - Find and Treat cases would be lost to follow-up at the same rate as enhanced tuberculosis surveillance controls (17.2% per year) in the absence of the service, rather than at the higher rate we estimated for this extremely hard to reach group (34.7% per year). - Even without Find and Treat involvement, these cases could still passively re-engage	has a net cost of £1.4 million and gained 220 QALYs - Incremental cost effectiveness of the Find and Treat service was £6,400/QALY gained - Both components of the service are cost-effective at the same threshold. The mobile screening unit had an incremental ratio of £18,000/QALY gained, whereas the case management component had an incremental ratio of £4,100/QALY gained (In the most unfavourable (and highly unlikely) scenario, which combined all the unfavourable assumptions, the mobile screening unit and case management components had incremental ratios of £26,000/QALY gained and £6,800/QALY gained, respectively) 0.5% of mobile screening unit patients	**Evidence gaps and/or recommendations for future research:** Include a larger intervention group, longer follow up study **Source of funding:** Grant from the English Department of Health grant reference number 0150305 PJW was partly funded by centre funding from the Medical Research Council. IA and HS are partly funded by the National Institute for Health Research. **Conflict of interests:** None

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			with treatment at the same rate as enhanced tuberculosis surveillance controls (51% per year). **Time horizon:** Sep 2007 – July 2010	and 5.3% of other Find and Treat patients had multidrug or extensively drug resistant infection	

List of Abbreviations

aOR = adjusted Odds Ratio; CDP = Chest Disease Centre; CHW = Community Health Worker; CXR = Chest X-Ray; HIV = Human Immunodeficiency Virus; IQR = Inter-Quartile Range; MXU = Mobile X-ray Unit; NA = Not Applicable; NIHR = National Institute for Health Research; NR = Not Recorded; OR = Odds Ratio; p = p-value; PTB = Pulmonary Tuberculosis; QALY = Quality Adjusted Life Year; TB = Tuberculosis; TBTCP = The Barcelona TB Control Program; TST = Tuberculin Skin Test; UK = United Kingdom; VNdG = Vila Nova de Gaia; 95%CI = 95% Confidence Interval

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1. Aldridge RW, Hayward AC, Hemming S, et al. Effectiveness of peer educators on the uptake of mobile X-ray tuberculosis screening at homeless hostels: a cluster randomised controlled trial. *BMJ open* 2015; **5**: e008050.
2. Goetsch U, Bellinger OK, Buettel KL, Gottschalk R. Tuberculosis among drug users and homeless persons: impact of voluntary X-ray investigation on active case finding. *Infection* 2012; **40**: 389-95.
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4. Duarte R, Santos A, Mota M, Carvalho A, Marques A, Barros H. Involving community partners in the management of tuberculosis among drug users. *Public Health* 2011; **125**: 60-2.
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Supplementary Material VI: Quality Assessment

Quality assessment of included effectiveness studies

	Questions about:	Population			Method of selection					Outcomes					Analysis				Summary		
Year	First author (year)	1·1	1·2	1·3	2·1	2·2	2·3	2·4	2·5	3·1	3·2	3·3	3·4	3·5	4·1	4·2	4·3	4·4	5·1	5·2	Score
Studies identified for this review																					
2011	Duarte et al.[5]	++	+	-	NA	+	++	-	++	+	+	-	+	++	NA	+	-	+	-	-	-
2012	Goetsch et al.[20]	++	+	-	NA	+	++	-	++	++	-	-	NA	NA	NR	++	-	-	-	-	-
2012	Ospina et al.[21]	++	++	++	++	++	++	-	++	+	++	-	NA	NA	++	++	-	++	-	++	+
2015	Aldridge et al.[19]	++	++	++	++	++	-	-	++	+	++	+	NA	NA	-	+	+	+	+	+	+
Studies identified for the NICE review[12]																					
2001	El-Hamad et al.[24]	++	+	++	NA	++	++	+	+	++	++	+	++	++	NR	++	+	++	+	+	+
2004	Deruaz & Zellweger[28]	++	+	+	-	+	-	-	+	-	++	++	++	++	NR	-	++	+	-	+	-
2008	Ricks[23]	++	+	++	++	++	++	++	+	+	++	++	++	+	NR	++	++	++	++	+	++

++	well designed study, minimal risk of bias
+	study may not have addressed all potential sources of bias
-	significant risk of bias
NA	not applicable
NR	not reported

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Quality assessment questions for effectiveness studies:

1·1 Is the source population or source area well described?
1·2 Is the eligible population or area representative of the source population or area?
1·3 Do the selected participants or areas represent the eligible population or area?
2·1 Selection of exposure (and comparison) group. How was selection bias minimised?
2·2 Was the selection of explanatory variables based on a sound theoretical basis?
2·3 Was the contamination acceptably low?
2·4 How well were likely confounding factors identified and controlled?
2·5 Is the setting applicable to Europe?
3·1 Were the outcome measures and procedures reliable?
3·2 Were the outcome measurements complete?
3·3 Were all the important outcomes assessed?
3·4 Was there a similar follow-up time in exposure and comparison groups?
3·5 Was follow-up time meaningful?
4·1 Was the study sufficiently powered to detect an intervention effect (if one exists)?
4·2 Were multiple explanatory variables considered in the analyses?
4·3 Were the analytical methods appropriate?
4·4 Was the precision of association given or calculable? Is association meaningful?
5·1 Are the study results internally valid (i.e. unbiased)?
5·2 Are the findings generalisable to the source population (i.e. externally valid)?

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Quality assessment of included cost-effectiveness studies

	Questions about:	Applicability								Study limitations											
Year	**First author**	**1·1**	**1·2**	**1·3**	**1·4**	**1·5**	**1·6**	**1·7**	**1·8**	**2·1**	**2·2**	**2·3**	**2·4**	**2·5**	**2·6**	**2·7**	**2·8**	**2·9**	**2·10**	**2·11**	**Overall**
Studies identified for this review																					
2011	Jit et al.[21]	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	**Potential serious limitations [+]**
Studies identified for the NICE review[12]																					
2002	Bothamley et al.[25]	PA	Y	Y	N	PA	N	N	PA	PA	U/C	PA	N	N	Y	N	N	Y	PA	N	**Very serious limitations [-]**
2006	Miller et al.[26]	Y	Y	PA	N	PA	N	N	PA	PA	PA	PA	PA	PA	PA	PA	PA	Y	Y	N	**Potential serious limitations [+]**
2008	Mor et al.[27]	PA	Y	PA	N	PA	N	N	PA	PA	PA	PA	N	PA	PA	U/C	U/C	Y	N	N	**Very serious limitations [-]**

Y	Yes to question
N	No to question
PA	Partially applicable
NA	Not Applicable
U/C	Unclear

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Quality assessment questions for cost-effectiveness studies:

1·1	Is the study population appropriate for the topic being evaluated?
1·2	Are the interventions appropriate for the topic being evaluated?
1·3	Is the system in which the study was conducted sufficiently similar to the current European context?
1·4	Was/were the perspective(s) clearly stated and what were they?
1·5	Are all direct health effects on individuals included, and are all other effects included where they are material?
1·6	Are all future costs and outcomes discounted appropriately?
1·7	Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?
1·8	Are costs and outcomes from other sectors fully and appropriately measured and valued?
2·1	Does the model structure adequately reflect the nature of the topic under evaluation?
2·2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?
2·3	Are all important and relevant outcomes included?
2·4	Are the estimates of baseline outcomes from the best available source?
2·5	Are the estimates of relative 'treatment' effects from the best available source?
2·6	Are all important and relevant costs included?
2·7	Are the estimates of resource use from the best available source?
2·8	Are the unit costs of resources from the best available source?
2·9	Is an appropriate incremental analysis presented or can it be calculated from the data?
2·10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?
2·11	Is there any potential conflict of interest?

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 and Supp Mat II
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup mat III
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, page 17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Sup mat VI and page 6, 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, 7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Sup mat VI
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			

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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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